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NUMBER 1

OBSERVATIONS ON BILIARY-PANCREATIC DYNAMICS IN A NORMAL HUMAN*

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INTRODUCTION

Studies on the dynamics of the human biliary system have usually been carried out on patients in whom a T tube was placed in the common duct at operation. These studies were directed at demonstrating the resistance of the sphincter of Oddi, or the visualization of the pancreatic duct by reflux of radio opaque medium. The validity of these observations was open to some criticism since the biliary tract was abnormal, and as a rule the gall bladder had been removed at operation.

THE PRESENT STUDY

An opportunity to carry out similar studies on a normal extra-hepatic biliary tract was presented to us in a 23 year old healthy male who developed a fistula from an intrahepatic duct following a bullet wound which perforated the liver. The patient discharged most of his bile into the intestine; about 100 c.c. drained each day through the fistula. By placing a Foley catheter into the fistulous tract and inflating the balloon about the catheter, a water tight seal was obtained. We were able to inject 35% diodrast into the catheter and outline the biliary tract roentgenologically. This demonstrated that the fistula connected with the right hepatic duct.

The following experiments were carried out:

1. *To demonstrate the effect of morphine on the sphincter mechanism.* 10 mgm. of morphine sulphate was injected subcutaneously. 15 minutes later diodrast solution (35%) was injected slowly into the biliary tract through the fistula leading to the right hepatic duct. Roentgen films were taken during this injection and during subsequent injections at 10 minute intervals. It was observed that: (a) the dye outlined the intrahepatic and extrahepatic ducts (Fig. 1) and partially filled the gall bladder at the first injection, (b) 30

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minutes after morphine administration, the gall bladder was completely filled and the terminal end of the pancreatic duct was visualized (Fig. 2), and (c) very little of the contrast medium entered the duodenum.

It was further observed that with each injection of diodrast and consequent distention of the bile ducts, epigastric pain and nausea occurred.

2. *To demonstrate the effect of amyl nitrite on the sphincter mechanism.* Immediately after the first experiment amyl nitrite was administered by inhalation. It was observed that (a) the sphincter mechanism which was rendered

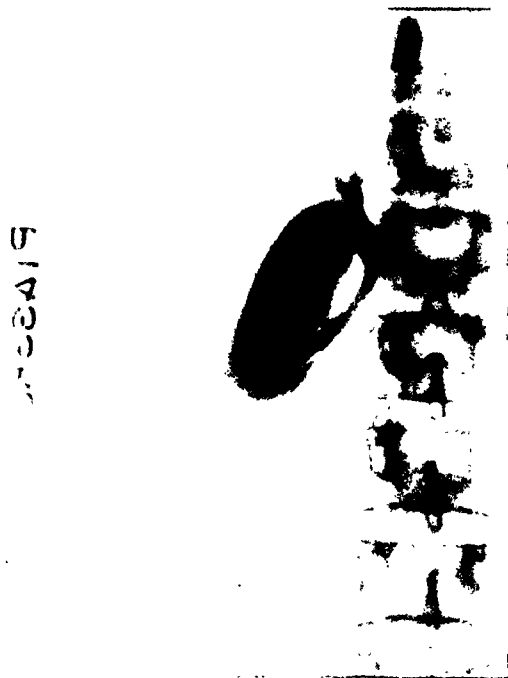


FIG. 1



FIG. 2

FIGS. 1 & 2. Injection of diodrast through Foley catheter lying in hepatic fistula connecting with right hepatic duct. 15 minutes after morphine, the biliary tract was outlined and the gall bladder was beginning to fill (Fig. 1). No diodrast has passed into the duodenum. Continued injection gradually filled the gall bladder and forced some diodrast into the duodenum (Fig. 2). The pancreatic duct was visualized (arrow). Note bullet lying in body of T 11. For purpose of clarity the terminal end of the ducts in these reproductions were outlined.

spastic by morphine immediately relaxed and the injected diodrast passed rapidly into the intestine (Fig. 3), (b) 5 minutes later the common duct was completely emptied and could not be visualized (Fig. 4), and (c) the gall bladder relaxed and did not empty.

3. *To demonstrate the effect of hydrochloric acid, applied locally, on the sphincter of Oddi alone.* Through a Rehfuess tube previously passed into the duodenum 10 c.c. N/10 hydrochloric acid was injected rapidly to create spasm of the sphincter of Oddi. Simultaneously diodrast was instilled slowly through the biliary fistula. Roentgen films were then taken.

It was observed that as a result of the spasm of the sphincter of Oddi, contrast medium was forced into the pancreatic duct (Fig. 5) thus demonstrating the common biliary-pancreatic passageway.

4. *To demonstrate the early effect of morphine on the sphincter mechanism and on the gall bladder.* Immediately following the above experiment 10 mgm. morphine sulphate was administered subcutaneously. 5 minutes later while diodrast was being injected, a Roentgen film was taken. It was observed that (a) the duodenal wall musculature was in spasm and compressed the lower end of the common duct (Fig. 6), and (b) the tonus of the gall bladder wall was increased.



FIG. 3



FIG. 4

FIGS. 3 & 4. Relaxation by amyl nitrite of sphincter of Oddi rendered spastic by morphine. The distended biliary tract emptied rapidly into the duodenum (Fig. 3). The bile ducts emptied so rapidly that they were no longer visualized 5 minutes after inhalation of amyl nitrite (Fig. 4). Note relaxation of the gall bladder and its failure to empty.

5. *To demonstrate by manometric recordings the effect of a fat meal on the intraductal pressure.* Normal saline solution was perfused into the biliary tract through the fistula at the rate of 1 c.c. per minute. This solution was siphoned off from the duodenum through a Rehfuß tube. A kymographic tracing of the intraductal pressure was made. When the system was stabilized 20 c.c. of a mixture of olive oil, cream and bacon drippings was administered through the duodenal tube. Later 10 c.c. of N/10 hydrochloric acid was injected through the duodenal tube to produce spasm of the sphincter of Oddi.

It was observed that (a) the intraductal pressure, as a result of the resistance of the sphincter, was 150 mm. of water (Fig. 7), (b) 2 minutes after the administration of fat the intraductal pressure rose and tonic contractions were recorded, (c) this pressure rise of 20 mm. of water occurred at the same time as the appearance of a flow of dark concentrated gall bladder bile from the Rehfuß tube, (d) after the production of spasm of the sphincter of Oddi by acid the intraductal pressure rose to 190 mm. of water and then fell rapidly as the hydrochloric acid effect wore off, (e) during this rise tonus rhythm



FIG. 5



FIG. 6

FIGS. 5 & 6. Visualization of pancreatic duct. Spasm of the sphincter of Oddi was produced by injecting acid into the duodenum through a Rehfuß tube (Fig. 5). Injection of diodrast through the fistula outlined the whole biliary tract and produced reflux up the pancreatic duct (arrow). Following this, a cholangiogram taken 5 minutes after morphine administration (Fig. 6) showed compression of the intramural portion of the common duct (arrow) and absence of pancreatic duct visualization. Note narrowing of the ampulla of the gall bladder in spite of increased pressure, due to action of morphine on the gall bladder musculature.

reappeared when the intraductal pressure attained 170 mm., and (f) the intraductal pressure gradually fell to 120 mm. at the termination of the experiment.

DISCUSSION

The observations on this patient with a normal biliary tract confirm the following facts previously reported^{1, 2, 3, 4} on postoperative patients who had disease of the biliary tract.

(1) Morphine causes spasm of the sphincter of Oddi (Fig. 8). This action

also includes the smooth muscle of the duodenal wall and gallbladder. The maximum spasticity of the sphincter occurs 5 minutes after administration of morphine. During this stage reflux of radio-opaque material into the pancreatic duct is difficult (Fig. 6), since the duodenal wall compresses the pancreatic

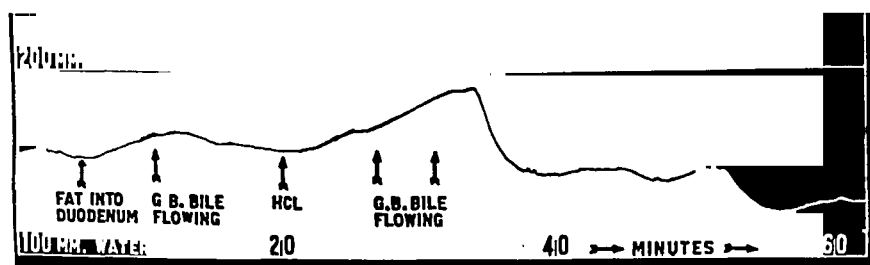


FIG. 7. Kymographic record of the intraductal pressure in a normal human extrahepatic biliary tract following a fat meal. 2 minutes after introduction of fat into the duodenum the pressure began to rise from a level of 150 mm. water and reached a maximum level of about 170 mm. in 5 minutes. Contraction of the gall bladder was evidenced by the appearance of thick dark bile in the duodenal siphonage. The sphincter was made spastic by injection of acid into the duodenum. The pressure then rose to a maximum of 190 mm. and fell precipitously at the end of 15 minutes as the effect of acid disappeared. Towards the end of the experiment the gradual decline of the intraductal pressure to 130 mm. indicated relaxation of the sphincter. The appearance of distinct tonus rhythm when the intraductal pressure registered 170 mm. was associated with the flow of gall bladder bile.



FIG. 8. Kymographic tracing of the resistance of the human sphincter of Oddi. Following the administration of morphine, gr. 1/6, the normal resistance of the sphincter (150 mm of water) rises to 300 mm and gradually subsides to 200 mm in one hour.

duct. 30 minutes later some relaxation occurs and reflux into the pancreas is possible (Fig. 2).

(2) Instillation of acid into the duodenum causes localized spasm of the sphincter of Oddi, but not of the duodenal wall (Fig. 9). This produces the

optimum condition for reflux into the pancreas (Fig. 5), as has been demonstrated repeatedly in operative cholangiography³. In the absence of the gall bladder the resistance of the sphincter rises to 250 mm., but in the presence of the gall bladder, the intraductal pressure rises only to 190 mm. (Fig. 7).

(3) Amyl nitrite produces immediate relaxation of smooth muscle even in the presence of spasm produced by morphine (Fig. 10). This explains the rapid emptying of the distended common duct (Figs. 3 and 4) as well as the relaxation and failure of emptying of the gall bladder.

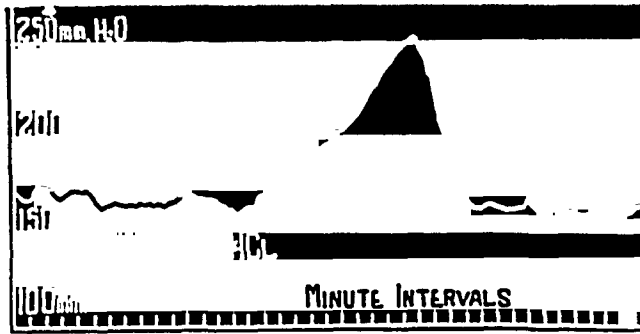


FIG. 9. The intraduodenal instillation of N/10 hydrochloric acid causes immediate spasm of the sphincter of Oddi. The resistance rises from about 150 to 250 mm of water and the effect wears off in about ten minutes.

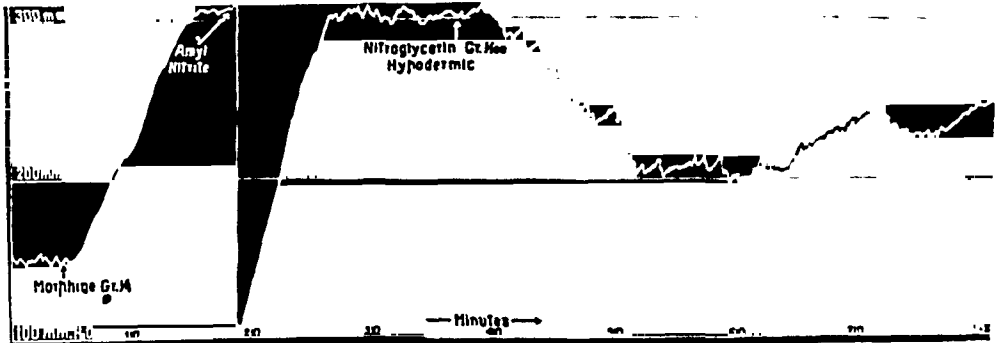


FIG. 10. The spasm of the sphincter of Oddi produced by morphine is instantaneously overcome by the inhalation of amyl nitrite. Note that the effect lasts only a few minutes. Nitroglycerine also causes relaxation but the effect, though not as great, is more prolonged.

The pressure regulating function of the gall bladder is demonstrated by the kymographic record of intraductal pressure during fat digestion. Previous observations⁴ of this function of the gall bladder were made only on animals^{5, 6}. This appears to be the first direct observation in man. Even in the presence of spasm produced by hydrochloric acid the intraductal pressure does not rise to the level found in the absence of the gall bladder.

Although the contractile force of the gall bladder could not be measured in this case, the appearance of tonus rhythm when the intraductal pressure at-

tained 170 mm. was of great interest. The similarity of this tracing to that observed previously⁷ in the gall bladder of the guinea pig and dog under the influence of cholecystokinin suggests that this tonus rhythm is due to contraction of the gall bladder. The appearance of gall bladder bile in the duodenal drainage tends to confirm this impression.

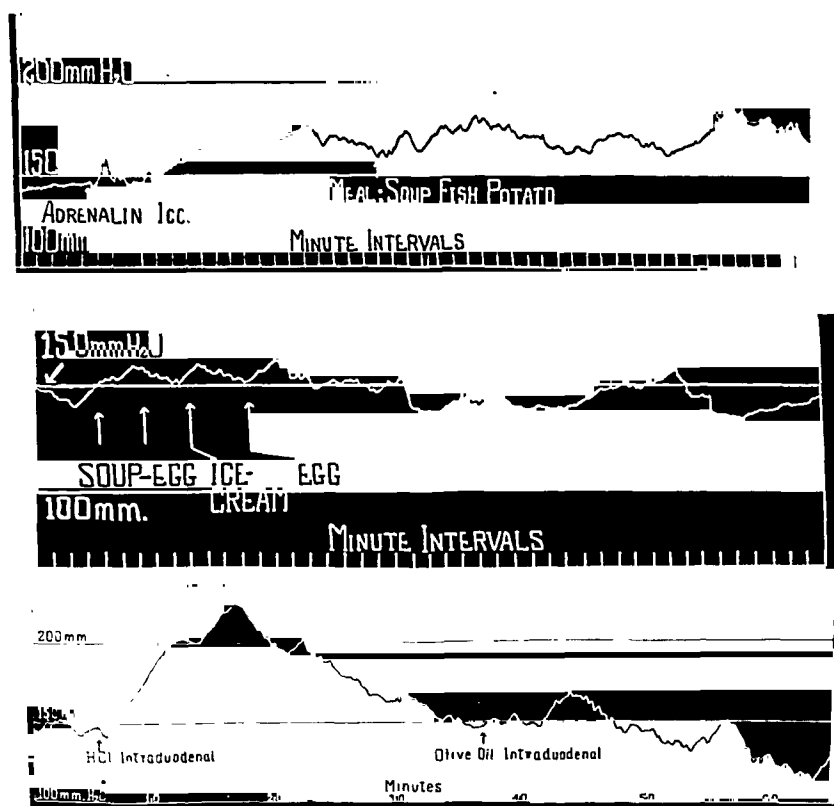


FIG. 11. The variations in resistance of the sphincter of Oddi following a meal. Note that in the first tracing the resistance increased slightly after the meal, in the second tracing there was a slight decrease in the resistance, while in the third tracing there was a considerable fall similar to that shown toward the end of the tracing in fig. 7. In these patients the gall bladder had been removed.

The decrease in intraductal pressure towards the end of the kymographic record is probably due to the relaxation of the sphincter of Oddi under the influence of cholecystokinin^{8, 9}. Our observations on the effect of a meal on the sphincter have been variable (Fig. 11).

CONCLUSION

1. Observations on a normal human extrahepatic biliary tract, using morphine, amyl nitrite and hydrochloric acid, were similar to previous findings in

cholecystectomized patients with a T tube in the common duct. This indicates that physiological observations on these patients are valid.

2. The small variations in intraductal pressure during the phase of contraction of the gall bladder in the normal human biliary tract, confirms previous observations on animals on its pressure regulating function.

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FLOCCULATION TESTS IN THE DIAGNOSIS OF HEPATO-BILIARY DISEASE*

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INTRODUCTION

In recent years a number of simple serologic flocculation reactions have been described for the demonstration of liver damage as well as for the differential diagnosis of jaundice. Almost all of these tests depend on the interplay of several factors such as qualitative and/or quantitative changes of serum albumin and increase in the serum gamma globulin, lipoproteins and/or lipids^{1, 2, 3}. Despite their similarity in principle, each test has a different basis. The question arises as to whether more information is obtained by the simultaneous performance of several of these tests than by any single test. This question concerns three problems: 1) the recognition of liver damage, 2) the differentiation of acute primary from chronic hepatitis, and 3) the differential diagnosis of surgical and medical jaundice. Similar studies have previously been carried out by several investigators, but most of them used fewer tests^{4, 5, 6, 7, 8}.

MATERIAL AND METHOD

On 324 subjects, 356 series of flocculation tests were performed and the results correlated with the clinical and other laboratory findings. The following flocculation tests were used:

(a) *Cephalin-cholesterol flocculation test*⁹. A two plus flocculation or more was considered pathologic.

(b) *Thymol turbidity test*¹⁰. The thymol turbidity was determined with the spectrophotometer calibrated with barium sulfate¹¹.† Serum diluted with buffer without thymol was used as a control. A turbidity above five but less than eight units was considered as slightly, while one above eight units as markedly abnormal.

* Supported by a grant from the Dr. Jerome D. Solomon Memorial Research Foundation, Chicago.

† The calibration was done with the barium sulfate suspension as described by Shank and Hoagland¹¹. This suspension has half the strength than it should have in comparison with the original standard curve of MacLagan¹⁰ since it is based on a 0.0962 normal instead of molar barium chloride solution. Consequently, the values reported here are twice as high as they should be on the basis of the original standard of MacLagan. However, since at present most reports are based on the Shank and Hoagland standard, the values in this paper were also recorded on this basis. Simple division by two of the values of thymol turbidity and zinc sulfate turbidity (which was also read with the same standard curve) would reduce the values to the ones based on the original standard of MacLagan.

(c) *Thymol flocculation test*. The method used⁷ is based on re-reading the thymol turbidity eighteen hours later and recording the second value as a percentage of the first. The turbidity may be reduced due to flocculation of some of the material producing it. If the second reading was less than 85 per cent of the first, the results were considered pathologic.

(d) *Gros test*¹². This test is based on a titration of diluted serum with Hayem's solution until flocculation develops. Flocculation before 2.25 cc. of Hayem's solution has been added was considered as slightly, while flocculation before addition of 1.75 cc. as markedly abnormal.

(e) *Takata-Ara test*^{13, 14}. This flocculation test, neglected in recent years, has been used because it seems to indicate a more severe and more chronic process in the liver as recently described by Alsted¹⁴ and as noted in our own work (data to be published). Flocculation in more than three tubes was considered abnormal.

(f) *Zinc sulfate turbidity test*^{16, 17}. This test is performed by diluting the serum with a buffered zinc sulfate solution. The turbidity thus produced is measured in the same manner as the thymol turbidity. A turbidity above 12.5 units was considered as evidence of a slight elevation, while one above 25 units as a marked elevation of the gamma globulins.

The material in this study consisted of (1) patients suffering from a variety of definitely established liver diseases; (2) normals (chiefly internes, nurses and technicians); (3) control patients (i.e. those suffering from local diseases not hepatic in nature, e.g. hernia and fracture) and (4) patients suffering from miscellaneous diseases such as pneumonia and infections in which hepatic involvement was not demonstrable. Usually only the first series of tests was considered.

RESULTS

1. *Differentiation of patients with and without liver cell damage*. (a) Results in different conditions. In normals and control patients, none of the tests were abnormal in a significant percentage. In patients with gastro intestinal or uncomplicated gall bladder disease, a slightly higher percentage of abnormal results was noted in the thymol and zinc sulfate turbidity tests. Twenty to forty per cent of the patients with miscellaneous diseases showed abnormal results in the different tests (Table 1). In the hepatic group—toxic or infectious—all tests with the exception of the thymol flocculation and Takata-Ara test were abnormal in the great majority of the cases. Patients with recovered hepatitis (tested two months to two years after the initial test) showed abnormal results in only some of the tests. Patients with cirrhosis, with slight or with marked jaundice gave abnormal results in most of the flocculation tests. The presence of marked jaundice did not significantly influence the results.

Patients with prolonged, but non-infected extrahepatic biliary obstruction (biliary hepatitis^{18, 19}) showed normal results in the cephalin flocculation and Takata-Ara tests. The thymol turbidity was abnormal in about 20 per cent and the Gros test in 60 per cent of these cases. The results of the zinc sulfate turbidity test were below the upper limit of normal. Patients with extrahepatic biliary obstruction complicated by bacterial infection of the portal triads (purulent hepatitis^{18, 19}) showed zinc sulfate turbidity levels in the range of the normal while the other flocculation tests with the exception of the Takata-Ara

TABLE 1

Percentage of abnormal results in flocculation tests in various diseases

DIAGNOSIS	NO. OF CASES	TEST								
		Ceph- alin floccu- lation	Thymol turbidity	Thy- mol floccu- lation	Gros test		Takata- Ara	Zinc sulfate turbidity		
		Assumed borderline								
		++	Above 5u.	Above 8u.	85%	Below 2.25 cc.	Below 1.75 cc.	+++	Above 12.5u.	Above 25.0u.
<u>Without liver damage</u>										
Normals	73	0	30.1	6.9	0	4.1	2.6	0	15.1	0
Control patients	14	0	28.6	0	7.1	7.1	7.1	0	28.6	0
Miscellaneous diseases	63	17.5	34.9	17.5	19.0	49.1	23.6	10.4	27.8	37.0
Gastro-intestinal diseases	13	0	7.7	0	0	30.8	7.7	7.7	7.7	0
Non-complicated gall bladder disease	13	0	30.8	7.7	15.4	38.5	7.7	0	15.4	0
Recovered hepatitis (not jaundiced)	16	0	50.0	18.8	25.0	43.7	0	0	62.5	18.7
<u>With liver damage</u>										
Infectious hepatitis	29	86.2	96.6	79.3	20.7	86.2	51.7	31.0	72.4	24.1
Toxic hepatitis	18	77.8	94.4	66.7	33.3	88.9	44.4	22.2	88.9	33.3
Cirrhosis with marked jaundice	42	71.4	73.8	50.0	31.0	97.6	88.1	90.5	88.1	47.6
Cirrhosis with slight jaundice	40	65.0	75.0	45.0	27.5	97.5	90.0	85.0	95.0	50.0
Biliary hepatitis	25	0	24.0	4.0	20.0	60.0	32.0	4.0	4.0	0
Purulent hepatitis	10	70.0	70.0	30.0	30.0	80.0	40.0	20.0	10.0	0

test gave abnormal results in the majority of the cases. All of these ten patients had fever ranging from 99.6°F. to 104.0°F., six had leucocytosis and four had chills.

(b) Results in groups with and without liver damage. The patients with liver cell damage (on the basis of biopsy, clinical findings and other liver function tests) gave abnormal results in the flocculation tests in 50 to 87 per cent of the cases with the exception of the thymol flocculation test. Patients without liver cell damage revealed abnormal results in less than ten per cent, if only

markedly abnormal values are considered (Table 2). A slightly elevated thymol and zinc sulfate turbidity and a slightly abnormal Gros test, however, were encountered in almost 33 per cent of the latter group. The relatively high incidence of abnormal results in patients without apparent liver cell damage reflects essentially the results obtained in the miscellaneous group. The comparatively high percentage of patients with liver cell damage who had normal results in the flocculation tests is explained by the inclusion of patients with biliary hepatitis in this group. Patients with liver cell damage differed from those without it also in the number of tests which yielded abnormal results. Thus, 64.3 per cent of the former had four or more and only 14.6 per cent had none or only one abnormal finding. In contrast, 70 per cent of the cases without liver cell damage had none or only one abnormal reaction while rarely did such a case have four or more abnormal findings (Fig. 1).

TABLE 2

Comparison of percentages of abnormal results in flocculation tests in patients with and without liver damage

DIAGNOSIS	NO. OF CASES	TEST								
		Ceph- alin floccu- lation	Thymol turbidity		Thy- mol floccu- lation	Gros test		Takata- Ara	Zinc sulfate turbidity	
		Assumed borderline								
		++	Above 5u.	Above 8u.	85%	Below 2.25 cc.	Below 1.75 cc.	+++	Above 12.5u.	Above 25.0u.
With liver damage	164	63.4	73.2	53.7	28.0	87.8	65.9	52.4	69.8	32.3
Without liver damage	192	5.7	31.8	10.4	9.9	27.1	10.4	3.7	23.4	13.5

(c) Specificity of the tests. This may be measured by a low incidence of abnormal results in normals and patients without obvious hepatic disease and a high incidence in patients with hepatic diseases. On this basis the cephalin flocculation test appears specific because it has a low incidence of pathologic results in patients without and a high incidence in cases with liver cell damage. A positive Takata-Ara and thymol flocculation test and a markedly elevated zinc sulfate turbidity test were rarely encountered in the absence of liver cell damage. These three tests, however, are not regularly positive in patients with liver damage. The Gros test is rarely positive in normals but has a high incidence of abnormal results in the miscellaneous group. The thymol turbidity test is frequently slightly elevated (five to eight units) in normals and controls but is regularly and markedly abnormal (above eight units) in patients with hepatic diseases. The zinc sulfate turbidity is rather non-specific because of the high incidence of elevated values in the normal and miscellaneous groups.

2. *Differentiation between acute hepatitis and cirrhosis.* In acute hepatitis

(toxic or infectious) the cephalin flocculation and thymol turbidity tests were slightly as well as markedly abnormal in a higher percentage than in cirrhosis (Table 3).

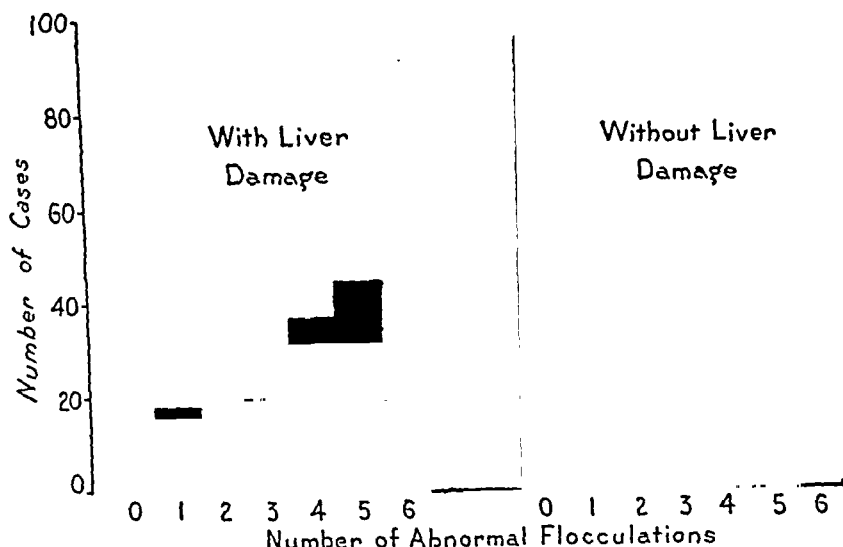


FIG. 1. Number of flocculation tests with abnormal results in cases with and without liver damage.

TABLE 3

Comparison of percentages of abnormal results in flocculation tests in patients with cirrhosis in contrast to those with acute primary hepatitis

DIAGNOSIS	NO. OF CASES	TEST								
		Ceph- alin floccu- lation	Thymol turbidity	Thy- mol floccu- lation	Gros test		Takata- Ara	Zinc sulfate turbidity		
		Assumed borderline								
		++	Above 5u.	Above 8u.	85%	Below 2.25 cc.	Below 1.75 cc.	+++	Above 12.5u.	Above 25.0u.
Cirrhosis	82	68.2	74.4	47.5	29.3	97.6	89.0	87.8	91.5	48.8
Hepatitis	47	83.0	95.7	74.4	25.5	87.2	49.0	23.4	57.4	37.6

In contrast, slightly or markedly abnormal results in the Gros, zinc sulfate turbidity and Takata-Ara tests were found more often in cirrhosis. The difference is especially striking if, in the Gros test, the lower, and in the zinc sulfate turbidity, the higher borderline is considered. Combining the results of the zinc sulfate turbidity, thymol turbidity and Gros tests and selecting pathologic borderlines at different levels led to a diagnostic system (Table 4). The as-

sumption of hepatitis, according to this system was confirmed in two thirds of the cases, while that of cirrhosis in almost 90 per cent. The addition of the

TABLE 4

Attempt to form a system using several flocculation tests in the differentiation of acute primary hepatitis from cirrhosis

The decrease in diagnostic errors which develops from the addition of the Takata-Ara test to the zinc sulfate and Thyrol turbidity and the Gros tests is indicated

ZINC SULFATE TURBIDITY	THYMOL TURBIDITY	GROS TEST	ASSUMED DIAGNOSIS WITH THESE TESTS	NO. OF CASES CORRECTLY CLASSIFIED	TAKATA ARA TEST	ASSUMED DIAGNOSIS WITH ADDITIONAL CONSIDERATION OF TAKATA ARA	NO. OF CASES CORRECTLY CLASSIFIED
Under 12.5u.		Over 1.50 cc.	Hepatitis	9 out of 10			
		Under 1.50 cc.	Cirrhosis	2 out of 2			
12.5u. to 25.0u.	Under 10u.		Cirrhosis	35 out of 47	Neg.	Hepatitis	10 out of 14
					Pos.	Cirrhosis	31 out of 33
	Over 10u.		Hepatitis	14 out of 16			
Over 25.0u.	Under 10u.		Cirrhosis	24 out of 28	Neg.	Hepatitis	4 out of 5
					Pos.	Cirrhosis	23 out of 23
	Over 10u.	Over 1.30 cc.	Hepatitis	7 out of 11			
		Under 1.30 cc.	Cirrhosis	14 out of 15			

Total error (considering all cases)

Without *With*
the use of the Takata-Ara Test

Cases of cirrhosis wrongly diagnosed as hepatitis 7 out of 82 (8.5%) 12 out of 82 (14.6%)

Cases of hepatitis wrongly diagnosed as cirrhosis 17 out of 47 (36.2%) 3 out of 47 (6.4%)

Takata-Ara test to this system reduced the incidence of false diagnoses of hepatitis but increased that of falsely diagnosed cirrhosis.

The relation between the results of the zinc sulfate and thymol turbidity test appears to have diagnostic importance (Fig. 2). In cirrhosis the zinc sulfate

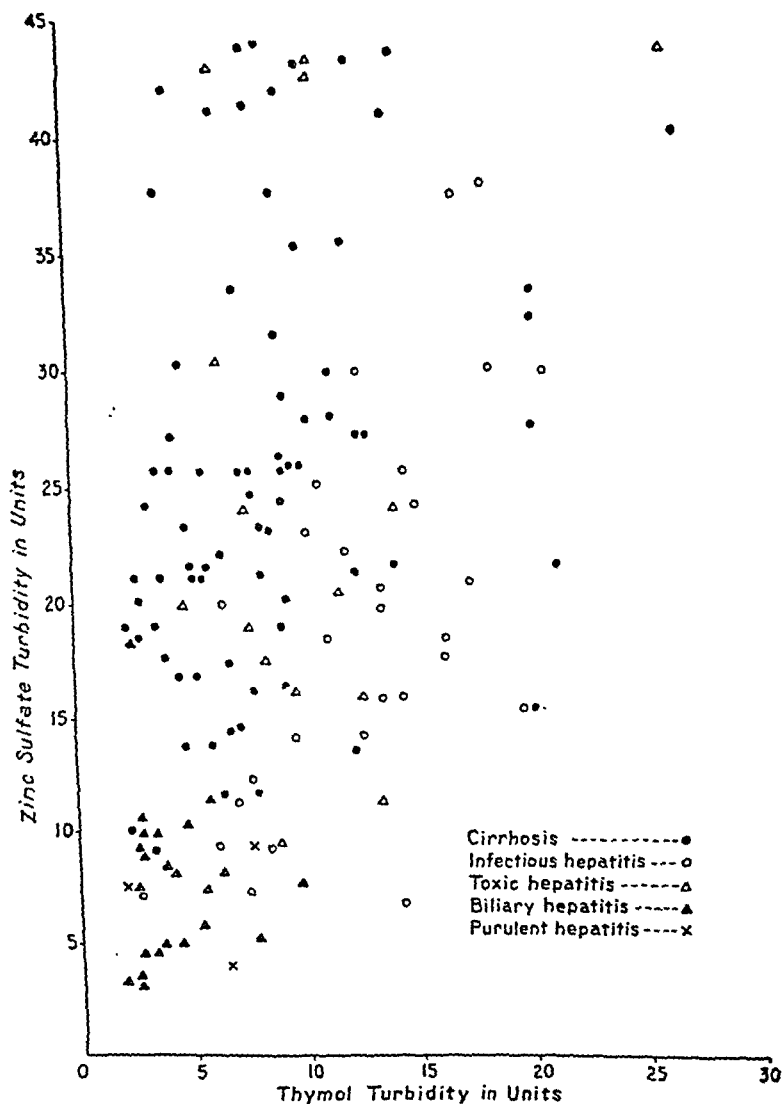


FIG. 2. Plot of results of the zinc sulfate and thymol turbidity tests in patients with various hepatic and biliary tract diseases.

turbidity is markedly elevated in face of only moderate rise of the thymol turbidity. In toxic, and even more so in infectious hepatitis, the thymol turbidity was markedly, while the zinc sulfate turbidity only slightly elevated.

3. *Differentiation between medical and surgical types of jaundice.* The results of the zinc sulfate turbidity test differed most strikingly in the two types of jaundice. Slightly less striking are the differences in the cephalin flocculation, markedly elevated thymol turbidity and the Takata-Ara tests (Table 5). In the slightly elevated thymol turbidity and the Gros test the differences are only suggestive, while they are non-existent with the thymol flocculation. If

TABLE 5

Comparison of the percentages of abnormal results in flocculation tests in patients with medical and surgical jaundice

DIAGNOSIS	NO. OF CASES	TEST								
		Cepha- lin floccu- lation	Thymol turbidity	Thymol floccu- lation	Gros test		Takata- Ara	Zinc sulfate turbidity		
		Assumed borderline								
		++	Above 5 u.	Above 8 u.	85%	Below 22.5 cc.	Below 1.75 cc.	+++	Above 12.5u.	Above 25.0u.
Medical jaundice	129	73.6	82.2	65.1	27.9	93.8	74.4	63.6	86.8	41.1
Surgical jaundice	35	20.0	37.1	11.4	22.8	65.7	34.3	8.6	5.7	0

TABLE 6

Attempt at a system for use of cephalin cholesterol flocculation and zinc sulfate turbidity in the differential diagnosis of jaundice

CEPHALIN CHOLESTEROL FLOCCULATION	ZINC SULFATE TURBIDITY	ASSUMED DIAGNOSIS	NO. OF CASES CORRECTLY CLASSIFIED
Negative	Under 12.5u.	Surgical	26 out of 29
	Over 12.5u.	Medical	39 out of 41*
Positive	Under 12.5u.	Medical	9 out of 16†
	Over 12.5u.	Medical	78 out of 78

* One of the two surgical cases was a biliary and one a purulent hepatitis.

† The error here is due to the inclusion of 7 cases of purulent hepatitis.

Total Error (considering all cases)

Per cent of medical cases wrongly diagnosed as surgical—2.3 (3 out of 129)

Per cent of surgical cases wrongly diagnosed as medical:

(a) including purulent hepatitis—25.7 (9 out of 35)

(b) excluding purulent hepatitis—2.8 (1 out of 35)

the purulent cases of extrahepatic biliary obstruction are omitted from the group of surgical jaundice and only the cases of biliary hepatitis (Table 1) are considered, the differences in the results of most tests become far more striking. An exception is the zinc sulfate turbidity, which is usually normal even in the face of bacterial infection.

A combination of two tests (cephalin flocculation and zinc sulfate turbidity) leads to a correct diagnosis in most instances (Table 6). Only 2.3 per cent of

the cases were wrongly considered surgical and 25.7 per cent were wrongly considered medical. However, if the cases of purulent hepatitis, which are clinically recognizable by evidence of sepsis, are omitted from consideration, the percentage of falsely assumed medical cases dropped to 2.8 per cent. The use of additional tests including the thymol turbidity did not significantly reduce the incidence of false diagnoses.

DISCUSSION

An evaluation of the results of flocculation tests can be based upon either the incidence of abnormal results or the degree of abnormality. In this paper more emphasis is given to the first viewpoint, since it appears of greater practical significance.

The flocculation tests appear of great practical value in the differential diagnosis between medical and surgical jaundice. Their value is based on the phenomenon that in non-infected, extrahepatic biliary obstruction they are, as a rule, negative or only slightly abnormal even if the liver damage is severe. No explanation for this phenomenon has as yet been established. If extrahepatic biliary obstruction is complicated by bacterial infection of the portal triads (purulent hepatitis) the flocculation tests become, as a rule, abnormal. However, since this condition is clinically indicated by septic manifestations (fever, chills and leucocytosis) it does not necessarily produce a problem in the interpretation of the results of the flocculation tests in the differential diagnosis between surgical and medical jaundice. For the differential diagnosis between surgical and medical jaundice, the zinc sulfate turbidity and the cephalin flocculation tests are of greatest value, the former especially because purulent hepatitis does not necessarily change it. The diagnostic results of a combination of both tests are superior to that of a single test, omitting almost all errors. The addition of the remaining flocculation tests adds little in this differential diagnosis.

The differentiation between acute hepatitis and cirrhosis is aided by the flocculation tests, though to a lesser degree than the differential diagnosis of jaundice. Although the Takata-Ara test, if taken alone, is of greater value than any other test, the lowest incidence of false diagnoses is achieved by combination of the zinc sulfate, thymol turbidity and Gros tests. The quantitative relationship between zinc sulfate and thymol turbidity is of added diagnostic significance since in hepatitis, markedly elevated thymol turbidity coincides with only moderate elevation of the zinc sulfate turbidity and the opposite holds true for cirrhosis.

Relatively little aid was derived from the flocculation tests in the differentiation of conditions with and without liver damage and in the differentiation of hepato-biliary diseases. A source of error lies in the fact that in biliary

hepatitis (liver cell damage in non-infected extrahepatic biliary obstruction) the flocculation tests may be normal or only slightly abnormal. On the other hand, almost all flocculation tests have a relatively high incidence of abnormal results in the miscellaneous group e.g. chronic infection or pneumonia^{17, 20, 21}; an abnormal flocculation test need not create a diagnostic problem since the primary disease is easily recognized. Similarly, in a patient with gastro intestinal symptoms abnormal flocculations do not necessarily point to primary liver disease. Of diagnostic importance may be the observation that with liver damage, more flocculation tests are abnormal than without. These considerations do not militate against the value of the flocculation tests in screening for liver cell damage or in the follow-up of a patient with established diagnosis.

In review, the cephalin flocculation test appears the most specific if positive, indicating liver cell damage due to primary hepatitis, cirrhosis or purulent hepatitis, whereas, the zinc sulfate turbidity test is most specific if negative in the presence of jaundice, excluding primary hepatitis or cirrhosis and pointing to a surgical type of jaundice. These two tests seem to deserve preference over the others. To differentiate cirrhosis from primary acute hepatitis and to recognize liver cell damage (not produced by biliary hepatitis) the additional use of thymol turbidity and also of the Gros and Takata-Ara tests appears justified. The thymol flocculation added little in this study.

SUMMARY

The cephalin cholesterol flocculation, thymol turbidity, thymol flocculation, Gros, Takata-Ara and zinc sulfate turbidity tests were performed on 324 persons, which included normals, patients suffering from miscellaneous diseases without conspicuous involvement of the hepato-biliary tract and patients suffering from diseases of this tract.

All flocculation tests have a significant number of abnormal results in miscellaneous diseases and some of them (e.g. thymol turbidity) even in normals.

Most of the flocculation tests, especially thymol turbidity, cephalin flocculation, zinc sulfate turbidity and Gros tests are as a rule normal or only slightly abnormal in liver cell damage produced by non-infected extrahepatic biliary obstruction (biliary hepatitis). With the exception of the zinc sulfate turbidity test they become abnormal if biliary hepatitis is complicated by bacterial infection of the portal triads.

The flocculation tests are of greatest value in the differential diagnosis between surgical and medical jaundice, especially the zinc sulfate turbidity and cephalin flocculation tests; more so even, if considered together and if secondary bacterial infection of the portal triads is accounted for by the clinical septic manifestation. The flocculation tests are of less value for the separation of acute hepatitis from cirrhosis. In this the Takata-Ara test is most helpful;

however, a combination of zinc sulfate and thymol turbidity and Gros tests reduces the number of errors.

The tests are of least value in the separation of conditions with and without liver cell damage except that a higher number of abnormal results in the different tests points to liver cell damage.

Of the tests studied the cephalin flocculation appears most specific if abnormal and the zinc sulfate turbidity if normal in the presence of jaundice. The additional performance of the thymol turbidity and Gros tests is helpful in the solution of most problems met in the differential diagnosis of hepato-biliary disease. Consideration of the results of several tests is advantageous over that of individual tests.

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GLUCOSE TOLERANCE IN PATIENTS WITH A PEPTIC ULCER*

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INTRODUCTION

The most prominent symptom complex exhibited by patients with a peptic ulcer is that of "hunger and epigastric pain between meals, relieved by food." This complex has also been commonly found in patients with hypoglycemia from various causes. Harris¹, in 1935, reviewed 200 cases in the literature in which he pointed out the frequent appearance of nausea, vomiting, and upper abdominal pain associated with extreme hunger, weakness, and drowsiness in patients with hypoglycemia from various causes. Many of these patients were admitted to the hospital with the unconfirmed diagnosis of peptic ulcer. Brown², in 1944, reported 10 cases of spontaneous hypoglycemia, of which 8 had epigastric pain as a prominent symptom.

Conversely, several investigators have attempted to determine whether a change in carbohydrate metabolism is a part of the pathological physiology involved in the picture of peptic ulcer. Abrahamson³ demonstrated the presence of a late hypoglycemia, below 66 mg. %, in patients with a peptic ulcer, during the fourth, fifth, and sixth hours of glucose tolerance test, using 100 grams of glucose and the Folin-Wu micro blood sugar method.

Most investigators who experimented in this field prior to Abrahamson's work did not use the full six-hour glucose tolerance test. Therefore, their results regarding a late hypoglycemia are not comparable. However, LeNoir, De Fossey and Richet⁴ and Van den Bergh and von Heukelom⁵ demonstrated another abnormality of the glucose tolerance curve in 50% of their ulcer patients, namely, a hyperglycemia above the expected normal level following the ingestion of 50 grams of glucose. More recently, Evenson⁶ found a rise above 180 mg.% in 61% of his ulcer patients as compared to 22% of his controls, using a 1.0 gram per kilo and a three-hour glucose tolerance test.

Further confirmation of the existence of a significant hyperglycemic reaction to the ingestion of glucose among ulcer patients is in the work of Christlieb⁷ which shows an average maximum value of 200 mg.% of sugar among 11 patients with gastric ulcer after the ingestion of 100 grams of grape sugar in a four-hour test. Furthermore, he found that four of his eleven curves subsequently fell to hypoglycemic levels below 60 mg.%. He was unable to demonstrate similar changes in 21 patients with duodenal ulcers.

* This study was aided in part by a grant from The Altman Foundation of New York City.

In contrast to the above investigation, Scherk⁸ found that nineteen patients with peptic ulcers had glucose tolerance curves which were almost identical to those of his controls in a two-hour test using 50 grams of glucose.

It is seen from the weight of evidence in the references above that the ability of the ulcer patient to handle ingested glucose is not normal. However, there is no agreement as to the specific differences which exist between the ulcer patient and the normal. Therefore, we have attempted to clarify these differences with a well controlled series and to extend the investigation in search of a possible physiological explanation.

METHOD

In our series, using 31 patients and 32 controls, we gave 100 grams of glucose in 50% aqueous solution. Venous blood samples were taken in the fasting state, one-half hour, one hour, and every hour for six hours in all cases. In 22 of our cases and 25 of our controls we took blood samples every fifteen minutes between the third and fourth hours to observe the hypoglycemic phase of the curve more closely. Blood sugar determinations were done by the Folin and Malmros⁹ method.

The symptoms of our patients and controls were recorded during the test, noting the time of their occurrence.

The results were analyzed statistically according to the method of Scott¹⁰.

CLINICAL MATERIAL

All patients had had a peptic ulcer previously demonstrated by a gastrointestinal x-ray examination. There were 29 cases of duodenal ulcer, 1 case of combined gastric and duodenal ulcer, and 1 case of gastric ulcer. X-rays were taken as closely to the time of the glucose tolerance tests as possible, and ulcers were classified as active or inactive, and no cases with pyloric stenosis⁶ or active bleeding were used. All patients and controls with liver or thyroid disease or any evidence suggestive of diabetes were excluded from this series. All patients were on a Meulengracht diet with a liberal carbohydrate allowance for several days prior to the glucose tolerance test. This was carefully observed because of the work of Conn^{11,12} and Sweeney¹³ who showed a marked hyperglycemia during glucose tolerance tests in normal patients after carbohydrate starvation. The tests were performed at least 12 hours after the last food eaten. The patients and controls were restricted to very mild physical activity while under observation¹⁴. The average age of the patients was 48 years, that of the controls 26. Although the extremes of age do have an effect on the glucose tolerance test, these patients fall well within the middle adult group where no changes are to be expected as a result of age¹⁵.

RESULTS

The results of our series, including 31 patients and 32 controls are seen in Figure 1. The average fasting levels of ulcer patients and controls were 101 mg.‰ and 97 mg.‰, respectively.

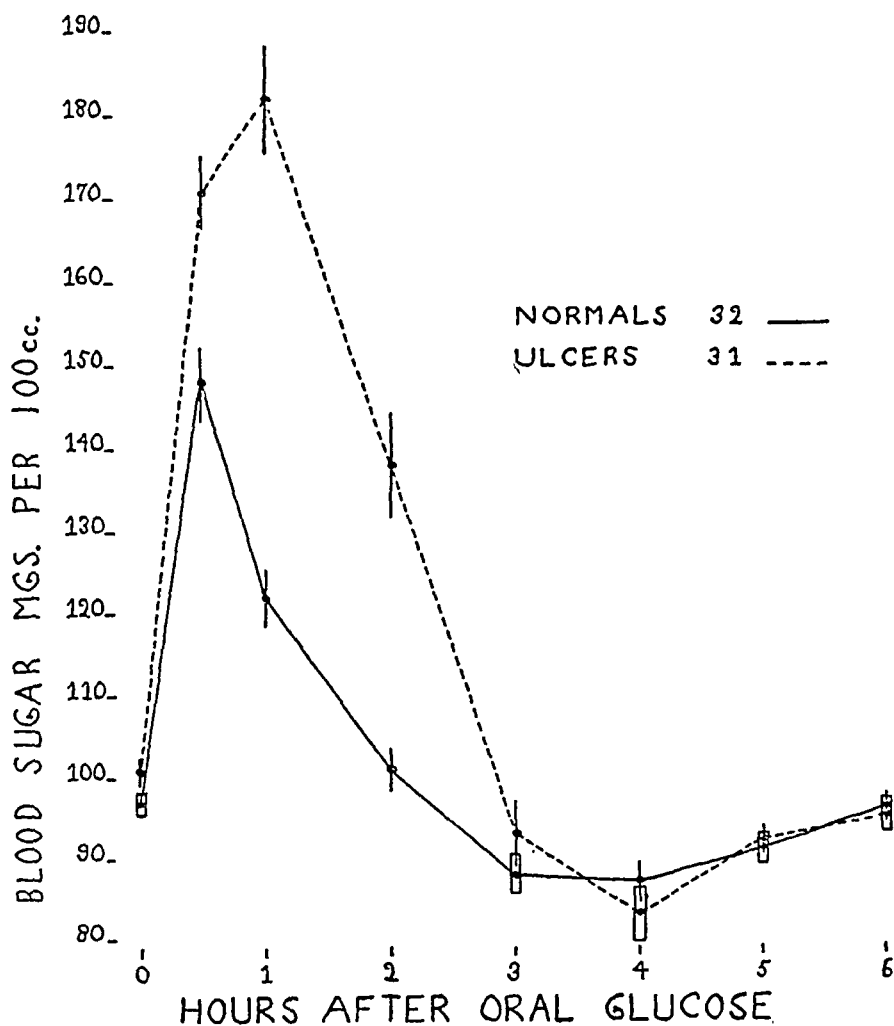


FIG. 1. Glucose tolerance curves of normal individuals and ulcer patients receiving 100 gms. of glucose orally. Figure in parenthesis indicates the number of subjects. The length of the vertical lines represents the mean deviation of the mean.

The most marked difference between the patients and controls was in the hyperglycemic peaks, the times at which these occurred, and the duration of the hyperglycemic phase. As seen in Figure 1, the peak of hyperglycemia reached 182 mg.‰ at one hour in the ulcer patient and 148 mg.‰ at one-half hour in the control, a difference of 34 mg.‰. In breaking down the figures, we found that 61% (19 out of 31) of the ulcer patients went above 180 mg.‰ as

compared to 11% (3 out of 32) in the control series. This figure for the ulcer series is identical to that found by Evenson⁶ in 50 patients, using 1.0 gram of glucose per kilo of body weight. 58% (18 out of 31) of the ulcer patients reached maximum hyperglycemia at one hour as compared to the control group where 97% (31 out of 32) peaked at $\frac{1}{2}$ hour. The rate of blood sugar change during hyperglycemia and the duration of hypoglycemia were greater in the ulcer than in the control series, resulting in significant differences between patients and controls at the one-half hour, the one- and two-hour values.

No significant difference could be found in the depth of hypoglycemia of the two curves, even when blood sugars were taken every fifteen minutes between the third and fourth hours (Table 1). However, on averaging the minimum

TABLE I
Comparison of blood sugar time curves

TIME AFTER ORAL GLUCOSE	BLOOD SUGARS	
	Normals (25)	Patients with ulcers (22)
<i>mins.</i>		
0	97	102
30	149	174
60	122	182
120	101	137
180	90	99
195	86	91
210	84	85
225	83	83
240	85	85
300	90	93
360	95	95

blood sugar values and disregarding the time factor, we found that the ulcer patients dropped 31 mg.% below the fasting level, whereas the controls only dropped 19 mg.% below fasting level. In comparing our values (Folin & Malmros method) with those derived from series using the Somogyi method¹⁶, which gives true sugar values, we did 24 determinations of the non-fermentable reducing substances in our specimens¹⁷ and found an average value of 15 mg.%. Therefore, the average minimum blood sugar value of 71 mg.% in the ulcer patient would be transposed to approximately 56 mg.% using the Somogyi method. In the control series, the lowest value would be transposed from 78 mg.% to approximately 63 mg.%.

No consistent differences between the types of curve produced in active as compared to inactive ulcer patients were apparent.

During the tolerance tests, we found that a combination of one or more of

the symptoms of hunger, drowsiness, headache, weakness, or dizziness occurred in all but one of the 21 ulcer patients questioned. The absence of epigastric pain during this period might be explained by the fact that we were careful not to do tolerance tests on patients during a period of pain.

The histories of the ulcer patients showed that in 81% (26 out of 30), hunger and pain occurred between three and four hours after eating and was often associated with weakness, headache, or drowsiness. These symptoms were usually allayed by taking food. In 33% (10 out of 30) of our patients, we found an excessive desire for and use of concentrated carbohydrate foods, such as candy.

This information would lead one to suspect that the appearance of symptoms in the tolerance tests between three and four hours was attributable to the presence of hypoglycemia. By the same token, it would make one think that the frequent symptoms of "hunger and pain before eating" in the ulcer patient were attributable to a reactive hypoglycemia from the previous meal.

In the control series, the symptoms were recorded in 23 persons. 65% (15 out of 23) of the normals complained of one or more of the symptoms of hunger, headache, weakness, or drowsiness between two and one-half and three and one-half hours. Our findings agree with those of Okada et al.¹⁸ who noted hunger in the hypoglycemic phase following the administration of glucose intraduodenally and intravenously in a four-hour test.

In order to explain the difference between our ulcer patients and controls and to eliminate the gastrointestinal factor, we did intravenous glucose tolerance tests on 15 patients and 15 controls. Eleven of each of these groups were included in our previous oral series. Twenty-five grams of glucose in 50% solution was injected in two minutes, and blood sugar levels were determined at fasting, five, fifteen, thirty, forty-five, and sixty minutes, and every half hour thereafter for four hours (Figure 2).

We found that the fasting, five, and fifteen minute specimens were essentially the same. After this, the two curves separated and the ulcer curve descended at a slower rate towards hypoglycemia. At forty-five and sixty minutes, the differences in the average blood sugar values were significant. The duration of hyperglycemia was 54 minutes in the controls and 115 minutes in the ulcer patients, calculated from the curves.

The calculated rate of fall in the ulcer patients from hyperglycemia to a fasting level is 1.4 mg.% per minute, compared to 3.2 mg.% per minute in the controls. The depth of hypoglycemia reached in the control curve, 87 mg.% or 14 mg.% below fasting, is slightly lower than that of the ulcer curve, 89 mg.% or 8 mg.% below fasting. When the individual minimal blood sugar values are averaged, regardless of time, that of the controls reaches 79 mg.%, or 22 mg.% below fasting, that of the ulcer series 85 mg.%, or 13 mg.% below fasting. Maximal hypoglycemia occurred at two hours in the controls and three hours in the ulcer series.

We recorded the symptoms in 8 patients and 14 controls during the test. In all of the patients and in 72% (10 out of 14) of the controls, we found one or more of the symptoms of hunger, headache, weakness, and drowsiness between

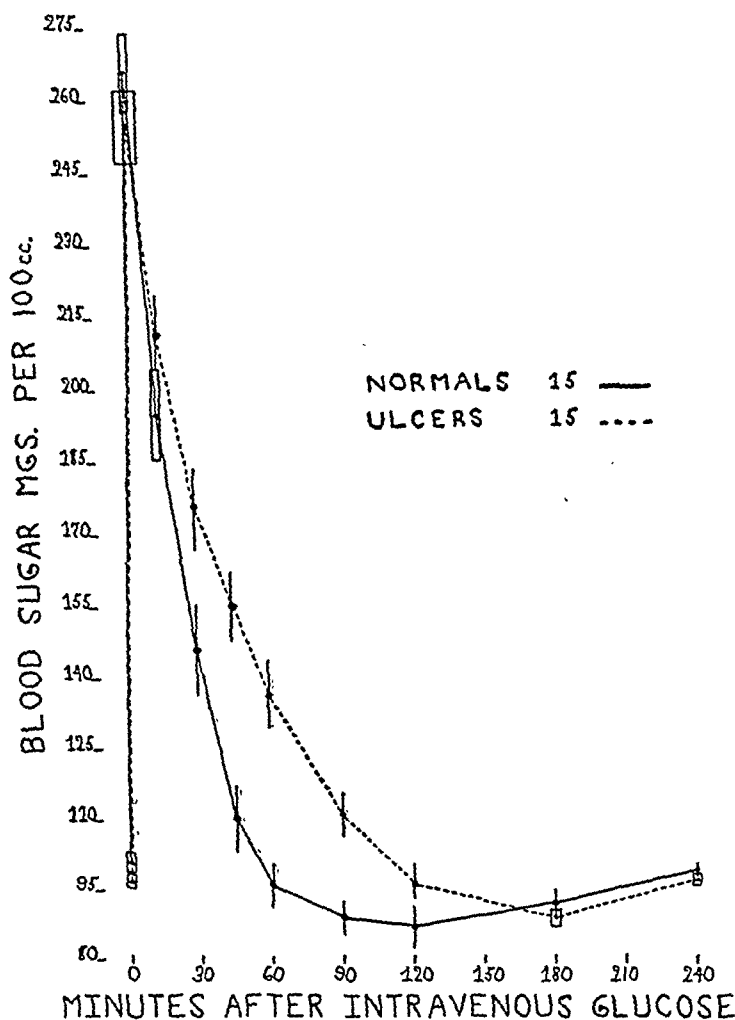


FIG. 2. Glucose tolerance curves of normal individuals and ulcer patients receiving 25 mgs. of glucose intravenously. The length of the vertical lines represents the mean deviation of the mean.

one and a half and three hours, corresponding with the low blood sugar values. The symptoms occurred earlier in the controls than in the patients with ulcers.

DISCUSSION

In attempting to analyze the differences between our patients and controls in the oral tests, we were first confronted with the problem of whether altered

gastrointestinal motility was responsible for the abnormally rapid initial rise of blood sugar (Figure 1). Evenson⁶ has performed periodic stomach aspirations on his ulcer patients during glucose tolerance tests and found that no definite relationship could be found between gastric emptying and the blood sugar curves. Under abnormal circumstances, when glucose is introduced into the duodenum very rapidly, as in patients with a gastroenterostomy^{6,19}, the blood sugar rises rapidly to abnormally high levels. However, in patients without this abnormal routing of gastric contents the blood sugar levels seem to depend more on the rate of utilization of the glucose after it enters the blood stream²⁰. This would seem to be the case in our ulcer patients, as evidenced by the prolonged hyperglycemia common to both the oral and the intravenous curves.

Ask-Upmark^{21, 22} found positive galactose tolerance tests in 34 out of 86 tests performed in patients with a peptic ulcer. He also found positive citric acid tests in 7 out of 22 cases. He interpreted his results as an indication of impaired liver function, but it will be noted that the galactose tolerance test, the glucose tolerance test, and the citric acid test all depend on one specific liver function, that of conversion of these substances to glycogen. This would indicate that either the liver impairment was confined to that function or that the poor utilization of these substances depended on a factor or factors outside of the liver.

Despite the evidence in the literature that diseases of the liver are frequently associated with peptic ulcers (Ask-Upmark²²) in common clinical experience, as in our series of 31 patients, there is no consistent evidence that liver disease is responsible for or present in the majority of cases of peptic ulcer. The glucose tolerance test in liver disease^{23, 24}, shows a marked fasting hypoglycemia, a high prolonged hyperglycemia, and a severe, prolonged, subsequent hypoglycemia. This type curve resembles that of our ulcer patients only in the hyperglycemic phase.

In comparing our ulcer curve with the ones produced following carbohydrate starvation²⁵, we note a striking similarity. The latter rises to hyperglycemic levels rapidly, the hyperglycemia is markedly elevated and prolonged, and the rate of fall to hypoglycemia is more rapid than in the normal. The depth of hypoglycemia reached is somewhat greater than that after an adequate carbohydrate diet, but the curves are identical after four and one-half hours. This description fits the curve of our ulcer patients almost exactly. We know that, normally, the respiratory quotient rises in response to ingested glucose as a result of increased tissue oxidation. However, in humans who have previously been deprived of an adequate carbohydrate diet, the respiratory quotient does not rise, indicating that tissue oxidation of glucose is reduced^{25, 26}. Under these circumstances, glycogen formation in the liver and muscles is unim-

paired²⁷. Since the curve after carbohydrate starvation and the ulcer curve are so similar, we may be dealing primarily with the factor of reduced tissue oxidation of glucose as an explanation for the abnormal tests in our patients, even though there was no previous carbohydrate deprivation. However, we cannot explain the fact that galactose tolerance is abnormal on this basis, for we know that galactose utilization depends on the liver, not on tissue oxidation.

We might suspect a pancreatic dysfunction as being responsible for the impaired utilization of glucose in our patients. Insulin causes a rapid drop of blood sugar in normal people²¹ and hyperglycemia will cause an increase in the production of insulin by a direct action on the pancreas^{18, 20, 27, 28}. In the absence of an immediate response to hyperglycemia, as in our patients, one might assume that a lag in the insulin response was present, due to a lack of insulin or to an insensitivity to insulin in the organs and tissues on which insulin acts. The former theory is not likely as the curve of a diabetic patient does not resemble the curve produced in our patients; the diabetic curve, having reached hyperglycemia, descends to the fasting level at a very slow rate. In the oral tests on our patients, we noted a late, but fairly rapid descent of the curve towards hypoglycemia. It is possible, then, that the reaction to hyperglycemia in the ulcer patient is normal in respect to the production of insulin but that the tissues upon which insulin acts are relatively insensitive to it. This might also explain why the resultant hypoglycemia in the ulcer patients was somewhat lower than in the controls, if we assume that an excessive amount of insulin is produced to overcome the tissue insensitivity, for the hyperinsulinism produced may have caused a prolongation of the descent into hypoglycemia by inhibiting glycogenolysis in the liver²⁰.

We know from the work of Soskin and Allweiss^{29, 30} that a normal glucose tolerance test can be produced in the depancreatized dog, given a constant amount of glucose and insulin. This experiment indicates that the fall to hypoglycemic levels is not directly due to an increase in the production of insulin. The fall to hypoglycemic levels, in the presence of a constant amount of insulin, can be explained by a reduction in the amount of glucose delivered to the blood by the liver as a response to the previous hyperglycemia. However, this obviously does not mean that a change in the amount of insulin will not influence the course of the glucose tolerance test. Experience with diabetics and normal people shows that increasing doses of insulin will cause a proportional fall to hypoglycemia. Therefore, our supposition that hyperinsulinism may have occurred in our patients as a result of the abnormal hyperglycemia is not incompatible with the above experiments or with the type of curve which was produced in our ulcer patients. However, we do not find the dramatic hypoglycemia which occurs in the usual case of hyperinsulinism either

because of a lack of sensitivity to insulin in the liver and tissues, a specific impairment in the ability to utilize glucose in the organs themselves, or a lack of some other factor governing carbohydrate metabolism. Again, the fact that galactose tolerance, which is unaffected by insulin and which is dependent on the liver alone for utilization, is also impaired indicates fairly definitely that at least part of the fault lies in either impaired liver function or in another factor governing carbohydrate metabolism. This does not indicate that a lack of insulin sensitivity cannot be present also, as one condition might follow the other.

E. J. Horgan³¹ discovered hypertrophic changes in the islets of Langerhans in 25% of his 71 cases of gastric ulcer and in 31% of his 71 cases of duodenal ulcer at autopsy. The changes consisted of an increase in the number of differentiated as well as undifferentiated cells. None of these patients had demonstrated glycosuria before death. These findings may indicate that the insulin producing mechanism had been hyperactive before death.

None of our patients had renal glycosuria or obvious disease of the thyroid, adrenals, hypophysis, or gonads, which can produce changes in carbohydrate metabolism²⁵.

The symptoms attributed to hypoglycemia in our patients and controls occurred at relatively high levels. Various values for blood sugar, done by various chemical procedures, have been given as the levels necessary to produce hypoglycemic symptoms. Harris³² gives the values of 75 mg.% to 60 mg.% for mild, 60 mg.% to 50 mg.% for moderately severe, and below 50 mg.% for severe hypoglycemia. In our oral tolerance tests, we found that 39% (12 out of 33) of our ulcer patients and 41% (13 out of 32) of our controls went to a level below 75 mg.% in the hypoglycemic phase. The value of 75 mg.% Folin-Malmros would be transposed to 60 mg.% using the Somogyi technique. However, we found a much greater incidence of symptoms than the blood sugar levels would suggest. The symptoms were mild, to be sure, but they were definitely present. This information, then, leads us to suspect that hypoglycemic symptoms occur normally during a six-hour glucose tolerance test even though the blood sugar levels do not reach so-called pathological levels³³. The fact that these symptoms occurred slightly more frequently in the ulcer patients may be due to the slightly lower hypoglycemic levels or to a relative hypersensitivity of the ulcer patients to hypoglycemia.

SUMMARY

1. The presence of abnormal glucose tolerance was demonstrated in ulcer patients using both the oral and intravenous routes of administration.

2. The results of the tests would seem to indicate that the abnormality was dependent on faulty post-absorptive utilization of glucose, rather than on a gastrointestinal factor.

3. Possible physiological mechanisms to explain these findings are discussed.

We would like to acknowledge the help of Dr. C. Louis Gilbert in securing the patients for this study and also the invaluable assistance of Miss Stephanie J. Ilka throughout this work. We are indebted to members of the house staff of St. Luke's Hospital who acted as controls in our studies.

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MECKEL'S DIVERTICULUM

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INTRODUCTION

In 1933 C. W. Mayo wrote: "Meckel's diverticulum is frequently suspected, often looked for, and seldom found." In this study we propose to analyze salient features of this disorder and add data on fifteen cases which we have found at operation.

Johann Friedrich Meckel^{4, 20}, a German comparative anatomist, (1781-1833) was one of the early discoverers of this anomaly although Levater in 1671 reported a diverticulum of the terminal ileum. Ruysch in 1707 gave an illustration of a diverticulum of the terminal ileum in his *Thesaurus Anatomicus*. Meckel, however, deserves credit for associating diverticula of the terminal ileum with the omphalomesenteric duct and observing their association with other congenital anomalies as cleft palate, harelip and bicornate uterus¹⁶.

EMBRYOLOGY

Meckel's diverticulum results from incomplete obliteration of the vitelline or omphalomesenteric duct in early fetal life^{16, 18}. Obliteration may be incomplete any place along the duct but when the segment adjoins the intestine the diverticulum is found. The proximal end of the yolk stalk becomes obliterated beginning about the fifth fetal week⁶. The obliteration of the stalk which begins in the fifth fetal week usually is completed about the seventh fetal week. When this does not occur then anomalies develop. If there is no closure a fistula discharging bowel contents at the navel may result. If the obliteration involves all but the distal portion then a fistula discharging secretion of the glandular elements at the umbilicus persists and in rarer instances each end of the stalk may obliterate leaving a patent middle portion and accumulated secretion may form a retention cyst or enterocyst. By far the most common anomaly is the diverticulum. These may vary in size from a mere cupola to a projection 30 cm. long. The site of a diverticulum varies from the ileocecal valve to about 90 cm. proximal to this junction, although Nygaard and Walters²¹ believe "Meckel's diverticulum may occur from the cardia to the rectum." In none of the fifteen cases in this series was an enterocyst or umbilical fistula present. In only one case (case No. 1) was a cord attached at the navel and the apex of the diverticulum. (See table I.)

Heterotopic tissue occurs in about 25% of all Meckel's diverticula²¹. Four theories have been recently advanced to explain the presence of gastric, pancreatic or duodenal tissue in this anomaly.

TABLE 1
Digest of pertinent data regarding fifteen cases in this study

CASE	INITIALS	SEX	AGE	ABD. PAINS	EMESIS	DURATION SYMPTOMS	MELENA	DIVERTICULUM CAUSED SYMPTOMS	SYMPTOMS RELIEVED BY OPERATION	POST-OPERATIVE DIAGNOSIS	END RESULTS
1	C. M.	M	24 yrs.	Yes	Yes	5 wks.	No	Yes	Yes	Intestinal obstruction from Meckels diverticulum	Recovery
2	L. K. H.	M	2 days		Yes	2 days	Yes	No		Congenital defect abdominal wall Meckels diverticulum	Death
3	O. S.	M	34 yrs.	Yes	No	13 mo.	No	Yes	Yes	Appendicitis and Meckels diverticulum	Recovery
4	G. D.	M	18 yrs.	Yes	No	1 day	No	No		Acute catarrhal appendicitis Meckels diverticulum	Recovery
5	L. P.	F	18 yrs.	Yes	No	3 days	No	No		Acute appendicitis Meckels diverticulum	Recovery
6	A. C.	F	27 yrs.	Yes	No	1 yr.	No	No		Meckels diverticulum Chr. appendicitis. Mucosa resembled gastric mucosa	Recovery
7	F. B.	F	31 yrs.	No	No	Symptomless	No	No		Uterine fibroid chr. salpingitis cystic oophoritis Meckels diverticulum	Recovery
8	D. S.	M	12 yrs.	Yes	Yes	1 day perforation	No	Yes	Yes	Perforated ulcer of Meckels diverticulum.	Recovery
9	B. B.	F	36 yrs.	Yes	No	5 mo.	No	No		Acute appendicitis, gastric mucosa Fibroid uterus. Bilateral salpingitis Meckels diverticulum	Recovery
10	L. S.	M	23 yrs.	Yes	Yes	4 yrs.	No	No		Meckels diverticulum gastric type mucosa chr. appendicitis	Recovery
11	M. M.	F	22 yrs.	Yes	No	Symptomless	No	No		Chronic appendicitis cystic left ovary Meckels diverticulum	Recovery
12	A. H. M.	M	46 yrs.	Yes	No	Symptomless	No	No		Adenocarcinoma gr. 4 rectum Meckels diverticulum	Death from ca. 1 yr. later
13	V. F.	F	33 yrs.	Yes	No	7 yrs.	Yes	Yes	Yes	Fibroid uterus Meckels diverticulum	Recovery
14	R. S.	M	18 yrs.	Yes	No	Symptomless	No	No		Acute appendicitis Meckels diverticulum gastric type mucosa	Recovery
15	N. H.	M	16 yrs.	Yes	No	2 days	No	Yes	Yes	Acute Meckels diverticulitis pancreatic tissue in Meckels	Recovery

Albrecht²¹ proposed that the endoderm lining of the primitive intestine possesses potentiality of developing into the glandular components of the fully developed gastrointestinal tract. This Albrecht called the pluripotential capacity of these cells.

Schartz²¹ proposed a transference or reimplantation theory of the endodermal cells lining the primitive intestinal tube. He suggested that the rotating movement of the embryo may have reimplanted these cells at the narrow points in the gastrointestinal tract.

Farr and Penke²¹ suggested that the vitello-intestinal duct originally may have had a digestive function hence it embodied a complete primitive digestive system. Finally Greenblatt¹¹ and his associates added their theory of dysembryoma. They agreed with Albrecht and Farr and Penke and went one step further and stated that while normally this embryonic system retrogressed as soon as its function ceased occasionally "a vestige of heterotopic tissue remained as a consequence of retarded embryological retrogression of the omphalomesenteric duct."

In three of the 15 cases of this series gastric type of mucosa was found in the microscopic sections. Cases number 6, 8, and 10 (see table). In one case (No. 15) pancreatic heterotopia was found.

INCIDENCE AND TYPES

Most authors agree that the anomaly occurs in about 2 per cent of autopsies and the sex incidence is about 3 males to 1 female.

Thompson in 1937 described six types of Meckel's²².

(1) Typical diverticulum given off from antemesenteric side of the ileum, lying free in the peritoneal cavity, 82.5%.

(2) Partial obliteration with a fibrous cord or band running from the tip of the diverticulum to the umbilicus or some adjacent structure, 10%.

(3) Umbilical fistula, 6%.

(4) Giant diverticulum often from the mesenteric side of the ileum developing between the folds of mesentery, 0.5%.

(5) Umbilical polyp either attached to the remains of the omphalomesenteric duct inside the abdomen entirely cut off from internal connection, 0.5%.

(6) Simple intramesenteric variety, 0.5%.

PATHOLOGY

The pathologic changes that one finds in a Meckel's diverticulum may vary from simple inflammation¹¹ to neoplasm. In six of our fifteen cases pathologic changes were found in the organ or in its position or environs. Hemorrhage from a diverticulum is one of the most common pathological changes accompanying this disorder³. Intestinal bleeding may occur with or without a definite ulceration of the diverticulum.

Inflammatory changes have been reported by Hiller and Bernhard after perforation of the Meckel's diverticulum wall by a rolled tomato peeling¹⁴. Williams in 1940 reported a case of a Meckel's diverticulum in a 62 year old male in whom a fish bone had perforated the wall and caused peritonitis³³.

Heterotopic tissue in a Meckel's diverticulum particularly if it is gastric type of mucosa is prone to ulcerate and cause bleeding or perforation, pancreatic tissue in the wall of a diverticulum however is rarely the site of pathologic change¹⁵. Because Meckel's diverticulum is an anomaly the most bizarre pathologic changes can take place. McCann has reported invagination of a Meckel's with partial obstruction of the ileum¹⁹. This author further suggested that some polyps of the small intestine take origin from an inverted Meckel's diverticulum.

H. N. Harkins¹³ collected from the literature and his own practice 160 recorded cases of intussusception due to invagination of a Meckel's diverticulum. From this large series of cases he was able to observe several distinguishing features of this type of intussusception. First it tended to occur in older individuals (average age 13.1 years). There was frequently a history of previous attacks and the course of the disease was more chronic and the patient might be mildly ill a day or two before the onset of the major illness. Vomiting was intense. If a mass was palpable it was likely to be in the right side of the abdomen and rarely was the mass palpable by rectum. Bleeding was less profuse from the rectum.

Gangrenous changes in a Meckel's may follow volvulus, invagination or intussusception and intestinal obstruction may accompany any of these conditions. Peritonitis may follow perforation, gangrenous changes or volvulus.

This diverticulum has been found in umbilical, inguinal and femoral hernias. Strohl and McArthur³¹ in 1939 reported two cases of Meckel's diverticulum in a femoral hernia and they reviewed the literature and found 147 cases had been reported by Watson in 1924—ninety six of these cases were in inguinal hernias—thirty-four were in femoral hernias.

A wide variety of benign and malignant tumors have been reported originating in Meckel's diverticulum. Polyps³⁰ and leiomyomas^{17, 29} have been reported. Nygaard and Walters²⁵ reported twenty malignant tumors of Meckel's diverticulum—fourteen of these were sarcomas and six carcinomas. Carcinoid tumors^{5, 27} have been described by several observers.

Gray and Kernohan¹⁰ reported a most unusual pathological condition in a Meckel's diverticulum, an intussusception and an adenocarcinoma arising in ectopic gastric mucosa.

CLINICAL SYMPTOMS

In discussing the clinical symptoms of Meckel's diverticulum some authors have suggested that before 25 years of age a certain group of symptoms are

more likely to obtain than in the older age group²³. In this early age group hemorrhage, perforation, volvulus, intussusception and intestinal obstruction are the most common clinical manifestations found. Crawford⁷ quotes: "Corriden who states that intestinal hemorrhage between the ages of 5-15 years are rare and that Meckel's diverticulum should always be suspected when one is confronted with melena during these ages." Chaffin³ reported 19 cases of Meckel's in children aged 17 hours to 8 years and intestinal hemorrhage was a symptom in 8 of the series. Perforation may follow a peptic ulcer and present the clinical picture of peritonitis. Three of Chaffin's cases presented this picture.

When a Meckel's diverticulum becomes inflamed it gives symptoms so much like appendicitis that either one rarely can be distinguished. Most of the symptoms from the diverticulum arise from the complication to which this anomaly is subjected³.

In this series of 15 cases inflammation was present in the diverticulum three times. One case (No. 15) revealed acute diverticulitis. One case (No. 1) revealed intestinal obstruction. One case (No. 8) revealed a perforated ulcer with a local peritonitis. In case No. 3 (see case report) dyspepsia and indigestion with abdominal distress were apparently caused by a Meckel's diverticulum and in case No. 13 (see case report) melena, cramping colicky abdominal pains were caused by a diverticulum.

In these cases severe melena was a symptom in two cases (Nos. 2 and 13). (See table I.)

In discussing clinical symptoms and diagnoses of Meckel's diverticulum, Brown and Pemberton² stated that a patient with an unexplained secondary anemia associated with a history of intestinal bleeding or with blood in the stools associated with roentgenologic evidence of a normal stomach and colon should arouse suspicion that there is an ulcer in the ileum or Meckel's diverticulum. Attacks of mild abdominal pain are customary yet they may not occur.

In the fifteen cases in the series five gave symptoms referable to the presence of the anomaly and these symptoms were signs of intestinal obstruction, chronic dyspepsia, perforated ulcer with local peritonitis, tarry stools and acute inflammation, diagnosed preoperatively as acute appendicitis. (See table 1.)

ROENTGENOLOGIC CONSIDERATION

In none of the fifteen cases in this series was a radiologic diagnosis made of Meckel's diverticulum. Pfahler²⁶ reported two cases of Meckel's diverticulum diagnosed by roentgen ray. The first was found February 2, 1923 and the second February 2, 1931. The first case was proved by operation, the second was not operated on.

The roentgenological characters of a Meckel's diverticulum according to

Pfahler were variable, but in general they were the same as any diverticulum. The sac cannot be filled with barium if it is already filled and peristalsis may be seen.

Ehrenpreis⁹ reported a Meckel's diverticulum diagnosed roentgenologically and proved by autopsy and Skinner and Walters²⁹ case was diagnosed roentgenologically before surgery. Hallendorf and Lovelace¹² reported a Meckel's diverticulum diagnosed by roentgenological examination of the colon.

SURGICAL CONSIDERATIONS

Uncomplicated Meckel's diverticulum rarely requires any surgical procedure except as it is accidentally found during a laparotomy and removed. One-third of the cases in this series (five patients) revealed symptoms or conditions due to the presence of the Meckel's diverticulum and these included intestinal obstruction (case No. 1), ruptured ulcer in Meckel's (case No. 8), diverticulitis (case No. 15), and melena (cases No. 2 and 13). In only three of these fifteen cases was a condition in the diverticulum the motivating element calling for the surgery. In most cases it was the complications of a diverticulum that demanded attention. Black and Packard¹ in discussing the surgical complications of this anomaly mentioned intussusception, hemorrhage, perforation and malignant changes as the most common and in this order.

The technical procedure involved in excision of a Meckel's diverticulum may vary from a simple ligation and excision to a large resection of small bowel in some of the gigantic diverticula⁸. Inversion of the stump of a diverticulum, as frequently practiced in an appendectomy, is sometimes undesirable in diverticulectomy because of encroachment of the inverted tissue on the lumen of the small bowel. If the base of the diverticulum is broad then excision with closure of the defect transversely to the long axis of the bowel may be desirable, and finally resection of the diverticulum and adjacent bowel with end to end or side to side anastomosis may be the best surgical solution. Entero-enterostomy around a narrowed small bowel lumen following diverticulectomy may sometimes be desirable. If the anomaly is accompanied by complications such as intussusception, intestinal obstruction or volvulus with gangrene, the surgical technical devices required to treat the condition most expeditiously are desirable, considering always the most important function of any surgical procedure is to carry the patient through the ordeal, cure his disease, and save his life.

SUMMARY AND CONCLUSIONS

Fifteen cases of Meckel's diverticulum were studied in this series, nine were males and six were females. All cases of the group were found at operation. The complications of Meckel's diverticulum (hemorrhage, intestinal obstruction, perforation) are frequently the conditions requiring surgical therapy rather

than the diverticulum itself. The presence of heterotopic tissue in the anomaly is common and important. In five cases in which symptoms were apparently caused by the presence of a Meckel's diverticulum all were relieved of symptoms by diverticulectomy.

ABSTRACT OF HISTORY

Case number 1. Clinic number 11711. C. M., male, aged 24 years, laborer, single. Usual childhood diseases and diphtheria, scarlet fever, pneumonia and typhoid fever all in youth. Peptic ulcer which improved under ulcer management 1936.

Present complaint paroxysmal pain right upper quadrant abdomen, nausea. Symptoms first noticed 4-5 weeks before admission when patient was lifting a post. Sudden, severe pain in upper quadrant of abdomen. Immediately was nauseated and vomited while standing holding to post. Pain in abdomen for 2 weeks after this gradually decreasing but still had residual soreness in abdomen. Two days before admission when he lifted again, got abdominal pain but not so severe.

Physical and laboratory findings. Blood hemoglobin 86% Sahli, erythrocytes 4.15 million, leucocytes 8,000, neutrophils 50%, lymphocytes 50%. Gastric acids, total 47, free 15. Gastrointestinal x-ray examination negative for gastric ulcer or diaphragmatic hernia.

Exploratory laparotomy May 24, 1936. When the abdomen was opened a loop of distended small bowel was noted. This was followed down to a Meckel's diverticulum which was red, inflamed and attached at the distal end at the navel. There was also a fibrous band which extended from near the base of the diverticulum to the posterior abdominal wall and a loop of small bowel distal to the diverticulum had slipped under this fibrous band and was partly obstructed. The diverticulum was freed from the navel, excised and the stump inverted without encroaching too much on the lumen. The appendix was bound down by fibrous adhesion, it was freed, removed, stump inverted. No ulcer could be found in stomach or duodenum, no other lesion found. Wound closed without draining. Risk 1+. Patient recovered, left hospital in 2 weeks. No symptoms referable to diverticulum after operation. Patient subsequently did have another duodenal ulcer which responded to medical management.

Case number 2. Clinic number 26684. L. K. H., 2 day old infant male. This child was a premature infant born with a congenital defect of the abdominal wall to the right of the navel. There was eventration through this defect of a portion of the large and small intestine. When a portion of the ileum was examined through the defect a Meckel's diverticulum was plainly visible.

Laparotomy October 2, 1941. Closure of congenital defect of abdominal wall. The defect in the abdominal wall was about 3 cm. in diameter to the right of the navel. The skin of the midline from the xiphoid to the defect and from the defect to the symphysis was infiltrated with 1% novocaine. A midline incision was made and the skin separated from the fascia and undermined. The eventration of small and large bowel was carefully replaced in the abdominal cavity. Child died two days after closure of defect.

Quotation from necropsy report: "A Meckel's diverticulum 1.5 cm. long, 0.4 cm. in diameter was found, 11 cm. from the cecum. The distal end of the diverticulum was attached by a fibrous cord to a neighboring loop of small intestine".

Case number 3. Clinic number 16655. O. S., aged 34 years, married, sheetmetal worker. Complained of vague abdominal discomfort for about one year, worse if ate rough vegetables, less on bland diet. Occasionally patient would have unexplained attacks of diarrhea, usually came on after eating. Physical examination was uninformative. No masses in abdomen, vague diffuse distress throughout abdomen. Laboratory data. Urine, sp. gr. 1020, acid, occasional pus cell. Blood examination: Hemoglobin 93% Sahli, erythrocytes 4.63 million, leucocytes 8,800, lymphocytes 46%, neutrophils 53%, eosinophils 1%. Gastric acids total 55, free 35. Kline negative. Roentgenogram of stomach was negative. Colon x-ray revealed spastic descending colon, tender over cecum.

Laparotomy July 13, 1939. Right rectus incision, negative exploration of stomach, duodenum and gallbladder. The appendix was removed in the usual fashion, stump inverted. A Meckel's diverticulum was found about 15 cm. above the ileocecal valve 5 cm. by 1 cm. This diverticulum was removed stump inverted. Risk 1+. Patient left hospital in 10 days. Recovered. No return of symptoms 10 years after surgery.

Case number 4. Clinic number 9438. G. D., male, aged 18, married, plumber. Past history was unimportant except for 4 or 5 attacks of appendicitis in the last 5 years. At work patient stopped over to pick up a bucket and noticed pain in the right lower quadrant abdomen, and in the back. Within two hours the pain became so severe that patient went home. Patient was seen at home in considerable abdominal pain, lying in bed with right leg drawn up, tender near McBurney's point on palpation. White blood cell count 11,000 and within two hours this had increased to 13,000. Temperature 99.0. No pathological changes in urine. A tentative diagnosis of acute appendicitis was made and the patient was admitted to the hospital.

Laparotomy May 17, 1941. Negative exploration of the gallbladder, stomach and kidneys. The appendix was long and its tip was grossly fibrosed. It was not inflamed. It was removed by clamping and ligation, stump not inverted. Search revealed a Meckel's diverticulum. This anomaly was approximately 15 cm. long and at first seemed to be a reduplication of the small bowel, however careful search revealed that it was a Meckel's diverticulum. Its blood supply was ligated separately and the diverticulum was removed, stump inverted. Risk 1+. Patient dismissed from hospital in 8 days.

Case number 5. Clinic number 7007. L. P., aged 18, single, student. Past history unimportant, never sick. Two days before admitted to the hospital had gradually increasing soreness right half of the abdomen. This was transitory and lasted only a few hours. On the day of admission she was awakened at 6 A.M. by pain in the right lower quadrant of the abdomen. This pain grew steadily worse as the day progressed. Coughing, straining at stool, climbing stairs caused distress in the right lower quadrant. General physical was negative except for slight right rectus rigidity

and soreness. Leucocyte count 14,000. Urine no pathological changes. Tentative diagnosis was acute appendicitis.

Operation February 9, 1940. The appendix was moderately inflamed and was removed in the usual fashion, stump inverted. There was a Meckel's diverticulum as large as the bowel about 20 cm. above the ileocecal valve. It was removed, stump inverted. Risk 1. Patient left hospital in one week.

Case number 6. Clinic number 26903. A. C., aged 27 years, single, factory worker. Past history thyroidectomy 1940. Tonsillectomy 1939. Influenza and pneumonia at age 5 years. Complained of nervousness for 3 years, fatigue 3 years and pain in the right lower quadrant for 1 year. For the past 3 years patient had been nervous, easily upset, crying spells, irritability, fits of depression. A thyroidectomy was done in 1940 but had no effect on these symptoms. Patient had been fatigued for 3-4 years. Has worked in factory 6 years and was completely exhausted.

Dull aching pain right lower quadrant of the abdomen present most of the time for past year aggravated by coughing or lifting. Loss of weight 10 pounds in one month.

Physical findings: A well developed, adult, white female, not acutely ill. Tenderness over McBurney's point. Negative pelvic examination.

Laboratory data: Urine sp. gr. 1015, acid, no pathological findings. Blood hemoglobin 79% Sahli, erythrocytes 4.06 million, leucocytes 6550, lymphocytes 37%, neutrophils 67%, basophiles 1%. Gastric acidity, total 35, free 20. Basal metabolism minus 6%. Barium enema—the colon fills completely and appears normal in contour and capacity. There is free filling of the terminal ileum. The appendix was not visualized, but there was definite tenderness localized to the mesial side of the cecum.

Operation November 17, 1941. Tentative diagnosis chronic appendicitis, explored pelvis. Appendix removed, stump inverted. Meckel's diverticulum found hands breadth above ileocecal valve. Meckel's excised. Risk 2+. Patient discharged from hospital 13 days.

Case number 7. Clinic number 7196. F. B., aged 31 years, married, housewife, 5 children living and well. Had rheumatic fever in childhood. Patient came to hospital for relief of vaginal bleeding 3 weeks post-partum. The patient had passed tissue resembling placenta 4 days before admittance to hospital and had continued to have vaginal bleeding since.

Physical findings revealed a well nourished young woman not acutely ill. The physical examination was unimportant except for vaginal bleeding and an enlarged uterus.

Pertinent laboratory data: Urine sp. gr. 1010, alkaline, pus and blood in urine. Erythrocytes 3.39 million, leucocytes 19,600, hemoglobin 74%, Mazzini negative.

A dilatation and curettage of uterus was done January 23, 1942, and a small piece of placenta was removed. A small uterine fibromyoma was found during vaginal examination under anesthetic. After consultation with patient and her family a pelvic laparotomy was decided on and this was done about a week later. In the course of this pelvic operation a Meckel's diverticulum was found and removed with

inversion of the stump, and patient left hospital two weeks later. The Meckel's diverticulum was symptomless and an incidental finding during the pelvic laparotomy.

Case number 8. Clinic number 26522. D. S., aged 12 years, school boy. This lad was a strong sturdy boy whose only illnesses had been childhood diseases. He was admitted to the Clinic Hospital during the night as an emergency and gave this history. He had been feeling fine, was working during the evening in a "pin ball booth" at the local street fair. After his evening meal he became acutely ill with abdominal cramps and went home about 9 P.M. The pain persisted and increased. At first it was in the upper abdomen. This distress finally localized in the right lower abdominal quadrant. The boy was brought to the hospital by his father who had decided the boy had appendicitis.

Physical examination revealed a sturdy, muscular boy, acutely ill. Temperature 100. Pulse 80. Respiration 20. The lad as he lay in bed would apparently have paroxysms of abdominal pain. During severe episodes of pain he would draw his legs up. There was exquisite tenderness in the right lower quadrant of the abdomen, and rebound tenderness.

Pertinent laboratory data: Urine, sp. gr. 1020, acid, no pathological findings. Blood hemoglobin 83% Sahli, leucocytes 17,000, erythrocytes 4.5 million. A tentative diagnosis of acute appendicitis was made and an emergency operation was decided on.

Operation September 24, 1941. The patient took the anesthetic very poorly and began to vomit a large quantity of food. Every effort was made to avoid aspiration. The peritoneum contained a few cc's of turbid bloody fluid. The appendix was moderately inflamed, it was removed and the stump inverted. Further search for abdominal pathology revealed an acutely inflamed Meckel's diverticulum, 5 cm. by 2 cm. about 20 cm. above the ileocecal valve. There was a small perforation near the tip of the diverticulum from which gas occasionally bubbled. There was a fibrinous exudate on the surface of the organ. The mesentery of the diverticulum was ligated and the organ was removed, stump inverted into the small bowel without excessively encroaching on the lumen. No other lesions found. Closure without drainage. The post operative course was stormy for a few days. Patient discharged in 10 days walking. Postoperative follow up revealed complete relief of symptoms.

Case number 9. Clinic number 9680. B. B., aged 26, married, housewife and mother of two living children. Her past history was unimportant. She complained of menstrual irregularity, nervousness, exhaustion, backache and bleeding from the rectum (bright red blood with movements). Physical findings were blood pressure 114/74, pulse 76 and temperature 99°. Enlarged tender uterus particularly on left side. Rectal examination revealed uterine enlargement, probably fibroid tumor. Laboratory examination revealed urine sp.gr. 1012, neutral, trace of bile, no albumin or sugar. Blood examination revealed hemoglobin 82% Sahli, erythrocytes 4.16 million, leucocytes 9500, neutrophils 82%, lymphocytes 16%, eosinophiles 2%, Kline negative and Friedman's test urine negative for pregnancy.

A tentative diagnosis of fibromyoma of uterus was made. At operation on March 2, 1935 a subtotal hysterectomy and left oophorectomy was performed. In the course of the operation a Meckel's diverticulum 5 cm. by 1 cm. was found and removed. Pathological examination revealed fibromyoma uterus, chronic salpingitis and Meckel's diverticulum. Patient had uneventful recovery and left the hospital about 10 days after hysterectomy, walking.

Case number 10. Clinic number 27578. L. S., aged 23 years, single, male, student. In his youth, age 18, patient had had poliomyelitis without any paralysis. Past history otherwise was unimportant. Patient entered clinic for a general "check up" and physical examination. This examination revealed no physical findings of significance except a right maxillary sinusitis which was treated by an otolaryngologist. A week later patient returned, he had gone back to school and been awakened in night with indigestion, epigastric pain, nausea. School doctor advised patient that he thought he had appendicitis and he returned to the clinic. Physical findings revealed blood pressure 130/80, pulse 84, temperature 99.2. Abdomen, no particular tenderness, cecum palpable, rectal negative. Laboratory data: Urine sp. gr. 1012, alkaline, no albumin, sugar or bile, 1+ phosphates. Blood icterus index 10, hemoglobin 91% (photometer), erythrocytes 5.34 million, leucocytes 10,600, neutrophils 64%, lymphocytes 36%, Mazzini negative.

A tentative diagnosis was made of subsiding appendicitis and patient returned to school. In the next three weeks patient had three similar attacks which his school doctor diagnosed as appendicitis and he was advised to enter hospital for appendectomy for chronic recurring appendicitis. When he entered the hospital the only findings were slight tenderness over McBurney's point and leucocyte count of 11,000.

Operation December 26, 1945. Negative exploration of gallbladder, pylorus and duodenum. The appendix was brought up into the wound and found to be beaded with fecal concretions and an appendectomy was done with ligation, no inversion of stump. Further exploration revealed a Meckel's diverticulum 4 cm. by 0.6 cm. There was no evidence of inflammation in the diverticulum. Diverticulectomy performed by ligation and without inversion. Sulfa powder dusted on stump. Patient left the hospital in seven days.

Case number 11. Clinic number 28316. N. M., aged 22, single, female, checker in supermarket, came to the clinic complaining of pain in the right side of the abdomen and hip. Vaginal discharge, swelling of feet, and exhaustion. There were no important data obtained from past history. The pain in the right lower abdomen and right hip came first several months ago, comes and goes, aggravated by being on feet—walking. Patient did this constantly at work. Pain was aggravated by constipation. Resting, especially in bed gave some relief. Vaginal discharge had been present for several months, yellowish-white always worse after periods. Swelling of feet came on as day wore on and by night feet were swollen, tender—swelling always disappeared over night. Physical examination revealed a blood pressure 120/80, pulse 100, temperature 98.6. Slender, linear type individual. Breasts tender before periods. Slight soreness over McBurney's point. Pelvic examination revealed cervical erosion, small upright uterus. Laboratory data—urine sp.

gr. 1023, alkaline, 2+ crystals, negative for albumin, sugar or bile. Blood hemoglobin 66% (photometer), sedimentation rate 2, erythrocytes 3.54 million, leucocytes 9,700, neutrophils 78%, lymphocytes 22%, Mazzini negative. Culture and smear from cervix revealed trichomonas vaginalis and no gonococcus in either smears or culture.

A barium enema revealed that "the colon completely fills and is generally ptotic with the cecum lying low in pelvis. There is an acute tenderness localized to the mesial border of the cecum. Film studies showed the appendix partially obscured by the terminal ileum. Conclusion: Ptotic colon—appendicitis questionable." An exploratory laparotomy was advised.

Operation May 22, 1942. A portion of the left ovary was cystic and this was removed. There was no gross change of the uterus, tubes and right ovary. The appendix was beaded with fecal concretion and was removed, stump inverted. A Meckel's diverticulum about 2 cm. by 0.5 cm. a few cm. above the ileocecal valve. It was removed, stump inverted without encroaching too much on bowel lumen. Closure in usual fashion in layers. Patient left hospital walking in 10 days.

Case number 12. Clinic number 34650. A. H. M., male. Aged 46, married, salesman. Came to the clinic complaining of backache and bleeding from the rectum at intervals for 8 months. The present complaint dated from an injury to the patient's back which occurred while he was lifting some heavy grain sacks. He was in bed about 10 days after the injury and then after this he suffered from backache, increasing constipation, and bleeding from the rectum. These hemorrhages were attributed by the patient to hemorrhoids. He had lost 30 pounds in weight for no apparent reason.

Physical findings, pertinent data: Height 72 inches, weight 217 pounds, blood pressure 135/78 pulse 78, temperature 98.6. Chronically infected tonsils. Dental abscesses proved by roentgenograms. Heart sounds normal. Lungs negative. There were no unusual masses or tenderness in the abdomen.

Laboratory data: Urine sp. gr. 1029, acid, no albumin, sugar or bile. Few pus cells in microscopic examination. Blood hemoglobin 79%, (photometer) erythrocytes 4.04 million, leucocytes 5,300, neutrophils 72%, lymphocytes 28%, Mazzini negative. Culture of stool revealed *B. coli* and streptococcus. A barium enema revealed a spasm of the sigmoid.

A sigmoidoscopic examination revealed a lesion encircling the sigmoid and a biopsy removed at this time revealed an adenocarcinoma grade 4. This established the diagnosis and the patient agreed to an exploratory laparotomy after preparation.

Operation. There was no gross involvement of the liver or the periaortic lymph nodes. The growth was extensive and filled most of the true pelvis, and the operability of the growth was in question and it was decided to do a double barrelled colostomy, Rankin type, and give the patient x-ray treatment and then re-explore him. This was done some weeks later after a series of x-ray treatments. At this second procedure the carcinoma was inoperable. A Meckel's diverticulum was found in the ileum and removed. The diverticulum was 10 cm. by 3 cm.

This patient died at his home from carcinoma about 1 year after the second operation.

Case number 13. Clinic number 59976. V. F., female, aged 33, married, housewife. Came to the clinic complaining of stomach and bowel trouble, nervousness, female trouble. Past history of disease was unimportant.

Seven years before entering the clinic this patient had a "nervous breakdown" and she had never enjoyed robust health since this illness. Before this illness she had low abdominal pain which she thought was related somehow to her genital organs. These disturbances usually came midway between periods and patient got some relief from lying cross-way on bed prone. Patient's appetite had been good but frequently after eating she had distress and pain through the abdomen. Most of the time this patient had the feeling of some sort of cramping or obstruction in the bowels and no kind of a cathartic seemed to give satisfactory relief for this feeling. Tarry stools have been present on several occasions.

Physical findings: Blood pressure 105/78, pulse 72, temperature 98.6. Patient was a well nourished, adult, female with no physical deformity. Heart sounds were normal. No enlargement of thyroid, no tremors. Abdominal palpation revealed no masses and no tenderness. Pelvic examination revealed a retroversion of the uterus and a mass posterior to the uterus which was thought to be a fibroid tumor of the uterus or a tumor of the ovary.

Laboratory data: Urine sp. gr. 1017, pH6, albumin, sugar and bile negative. Blood hemoglobin 88% (photometer), erythrocytes 4.46 million, leucocytes 4,550, neutrophils 58%, eosinophils 1%, lymphocytes 48%, Mazzini negative. Basal metabolism rate minus 1%.

Roentgenograms: Chest ray negative. Colon essentially negative. Appendix visualized by fluoroscopy. Gastrointestinal series—stomach, duodenum and esophagus revealed no disease in these organs.

A tentative diagnosis of fibromyoma of the uterus was made and the patient was advised to have a hysterectomy.

The uterus was retroflexed and retroverted, about twice normal size and apparently contained fibroid tumors. A supravaginal hysterectomy was done removing both tubes. The ovaries were not changed and were not disturbed. An appendix measuring 8 cm. by 0.8 cm. was removed with inversion of the stump. A Meckel's diverticulum was found 10 cm. above the ileocecal valve. The diverticulum was excised and measured 4.5 cm. by 1 cm. Microscopic examination of the Meckel's revealed no unusual structures.

This patient was in the hospital for 15 days. Her postoperative course was disturbed by abdominal distension and 4 days after surgery there were dark tarry stools. Patient dismissed in good condition. Patient was relieved of symptoms when last heard from two months after operation.

Case number 14. Clinic number 26341. R. S., male, aged 18 years, student, single. Complained that three or four days previously he began to have a continuous dull aching pain in the right lower quadrant of the abdomen. There was no nausea or vomiting, constipation or appetite change. Examination at home revealed minimal tenderness over McBurney's point and some rigidity of the right rectus muscle. There was also slight bilateral inguinal lymphadenopathy. The white count at

this time was 10,000. Four hours later the leucocytes numbered 12,000, and the patient entered the hospital.

Physical findings: Blood pressure 140/80, temperature 98.0 pulse 100. Patient was a well developed, well nourished, young male not acutely ill. No pathology found in head or neck. Chest sounds clear. Heart sounds revealed no abnormality. Examination of the abdomen revealed some right rectus rigidity and tenderness on pressure near McBurney's point. Rectal examination revealed tenderness on the right side.

Laboratory data: Urine—sp. gr. 1020, pH6, no albumin, no sugar, microscopic examination revealed no findings. Blood—hemoglobin 85% (photolometer), erythrocytes 4.2 million, leucocytes 12,000.

A tentative diagnosis of acute appendicitis was made and the patient was advised to have an appendectomy.

The appendix was visualized. It was inflamed near the tip and there were many enlarged inflamed mesenteric lymph nodes, particularly in the ileum. The appendix was removed after ligation and without inversion of the stump. Further search revealed a Meckel's diverticulum. This was about 15 cm. above the ileocecal valve and the diverticulum apparently arose from the lateral wall. Because of this and the wide base the diverticulum was excised between clamps. The diverticulum measured 5 cms. by 2 cm. Microscopic examination of the diverticulum revealed gastric type of mucosa in some areas. Recovery was uneventful and patient left hospital on seventh day.

Case number 15. Clinic number 61763. N. H., male, aged 16 years, single, student. Came to clinic complaining of pain in the right lower quadrant of the abdomen, which began the afternoon of the previous day. This pain was periodic and severe, "doubled patient up", lasted about one-half hour and disappeared spontaneously. A few hours later when patient bent forward the pain returned and had persisted ever since. A leucocyte count at this time revealed 7,700 cells. Physical examination revealed tenderness which was as great on release of pressure on the abdomen as during application of pressure. Rectal examination revealed soreness on the right side of the rectum but no mass.

The next morning examination at the clinic revealed the findings as given plus a tendency of the patient to walk slightly bent forward as though protecting his abdomen. There was no history of diarrhea or constipation, nausea or vomiting and the patient had had usual daily bowel movements.

Physical findings: Height 75 inches, weight 165 pounds, blood pressure 135/90, pulse 80, temperature 99.0, and the findings already described above. The remainder of the physical examination was uninformative.

Laboratory data: Urine—pH5, albumin 1+, bacteria 2+, pus 1+. Blood—hemoglobin 91% (photolometer), erythrocytes 4.32 million, leucocytes 10,100, neutrophils 64%, basophiles 2%, lymphocytes 34%.

A tentative diagnosis was made of acute appendicitis and an appendectomy was recommended and accepted by the patient.

There was no free fluid in the peritoneal cavity. There was no gross change of

the gallbladder. A retrocecal appendix which revealed no change was brought into view, and removed without inversion of the stump. A search was then made for a Meckel's diverticulum and one was found about 20 cm. above the ileocecal valve. It was acutely inflamed and measured 7 cm. by 2 cm. The diverticulum was removed.

Pathologic studies of the diverticulum revealed an acute inflammation of the organ with pancreatic tissue in the wall near the tip.

The appendix revealed no significant changes.

The patient had an uneventful convalescence and left the hospital in one week walking. He now is working in hospital as orderly and free of symptoms.

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HIATUS HERNIA AND CARCINOMA OF THE STOMACH AND ESOPHAGUS

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INTRODUCTION

In a recent study^{1, 2} of the incidence of hiatus hernia and associated lesions diagnosed by the roentgen ray, a review of the data revealed the infrequency with which gastric and esophageal carcinoma were associated with hiatus hernia.

Table 1 shows the essential material on which the present study was based. In a large general hospital, the X-ray reports of 3448 patients who had upper gastrointestinal barium examinations were studied. In this group of patients, 308 or 8.93% were shown to have a hiatus (diaphragmatic) hernia. This entity was the second most commonly diagnosed, duodenal ulcer occurring in 705 or 20.41% of the patients. In this unselected group, carcinoma of the stomach was diagnosed after roentgen study in 101 patients or 2.92%. That the patient material studied is not preponderantly in the elderly age groups is demonstrated by the diagnosis of duodenal ulcer, not uniquely a disease of the aged, in one of every five patients examined. While three types of hiatus hernia may be differentiated roentgenologically, in the present study no differentiation is made since the manifestations of all types are similar.

In the 308 cases of hiatus hernia, 79 associated gastrointestinal lesions were diagnosed, as shown in Table 2. The associated diagnoses are not included in the diagnoses in Table 1. It will be noted that while gastric carcinoma was diagnosed by X-ray in 4 patients, with hiatus hernia, clinical study revealed that only two patients actually had carcinoma. Details in these cases will be given below. One case of a carcinoma of the esophagus accompanying a hiatus hernia was also confirmed clinically.

Carcinoma of the stomach, then, occurred in 2.92% of all patients studied but in only 0.65% of the patients with hiatus hernia. Thus, in this rather large group of patients, carcinoma of the stomach occurred four times as frequently in the group without a hiatus hernia. Since 80% of the group with hiatus hernia were over the age of 50^{1, 2} this seems even more striking. It was, therefore, thought worthwhile to review the literature and present the clinical data in these cases of carcinoma accompanying hiatus hernia. The analogy with reference to duodenal ulcer and carcinoma of the stomach

comes readily to mind. It is the clinical impression of some authors that carcinoma of the stomach occurs much less frequently in patients who have duodenal ulcer. Fisher, Clagett, and McDonald³ review this subject quite thoroughly and confirm, in a series of cases of large proportions, the impression that patients who have duodenal ulcers rarely have gastric carcinoma. They were unable to reach any conclusion as to why this should

TABLE 1

Incidence of most frequent diagnoses in upper gastrointestinal roentgen examinations

	NO. OF PATIENTS HAVING UPPER GASTROINTESTINAL X-RAY STUDY	DUODENAL ULCER		HIATUS HERNIA		GASTRIC ULCER		CARCINOMA STOMACH	
		No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
1945.....	1619	315	19.45	140	8.64	50	3.08	41	2.53
1946.....	1829	390	21.32	168	9.18	70	3.82	60	3.28
Totals.....	3448	705	20.41	308	8.93	120	3.48	101	2.92

TABLE 2

Associated gastrointestinal lesions diagnosed by x-ray study in 308 cases of hiatus hernia

	No. of cases
Esophageal diverticulum.....	5
Esophageal varices.....	3
Esophagitis.....	3
Esophageal carcinoma.....	1
Gastric ulcer.....	2
Gastric carcinoma.....	4 (2)*
Gastric diverticulum.....	1
Gastritis, hypertrophic.....	7
Hypertrophy of pylorus.....	1
Duodenitis.....	3
Duodenal ulcer.....	31
Duodenal diverticulum.....	15
Jejunal diverticulum.....	3
Totals.....	79

* Clinical investigation of these 4 cases revealed that only two actually had carcinoma. The other two cases (one at operation and one at necropsy) did not have carcinoma of the stomach.

occur. One wonders whether this might also be true in patients who have hiatus hernias.

CARCINOMA OF STOMACH ASSOCIATED WITH HIATUS HERNIA

Moller⁴ presented a case, with necropsy, of a 62 year old male who had a carcinoma of the fundus of the stomach in association with a hiatus hernia. A thorough review of the world literature by Moller added six other such

cases reported prior to his. All save one case occurred in patients over the age of 50. The exception was a female of 27 who, in addition to a hiatus hernia, had a carcinomatous gastric ulcer which perforated. This latter case was originally reported by Watt⁵ who stated that the hernia of the diaphragm was traumatic, the result of a slide of sand falling on the patient 10 years previous to discovery of the diaphragmatic hernia. Including Moller's case, only two of the carcinomas were in the cardiac portion of the stomach.

TABLE 3

Summary of cases of hiatus hernia associated with carcinoma of stomach

AUTHOR	NO. OF CASES	HOW DIAGNOSED	PORTION OF STOMACH INVOLVED
Moller (4)	7*	Necropsy	2—Cardiac
Magnes and Clerf (6)	1	Clinically	Cardiac
Held and Goldbloom (7)	1	No data	Pyloric
Cowan (8)	1	Surgery	Antral
Jacobs (9)	1	Necropsy	Cardiac
Jankelson and Morein (11)	2	Clinically	2—cardiac
Holland and Logan (12)	1	Biopsy	Cardiac
Jackson (12)	"Few"	No data	
Beilin (13)	1	No data	
Christiansen (14)	1	Necropsy	Cardiac
Young (15)	1	Necropsy	No data
Murphy and Hay (16)	2	No data	
Harrington (17)	5	Surgery	4—no data 1—pyloric
Olsen and Harrington (18)	3	2—biopsy 1—surgery	3—cardiac
Smithers (19)	2	1—necropsy 1—no data	1—lesser curvature 1—cardiac
Dunhill (19)	3	No data	
Johnstone (19)	5	No data	
Warmoes and Pennewaert (20)	3	No data	
Mailer (21)	1	Surgery	Cardiac
Brick	2	1—surgery 1—clinically	1—lower third 1—pyloric

* Six cases from literature.

Table 3 summarizes the reported cases ^{4, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21} of associated hiatus hernia and carcinoma of the stomach and includes two cases being presented in this paper.

In reporting a confirmed case of carcinoma of the cardiac end of the stomach associated with a hiatus hernia, Jacobs⁹ remarked that the rarity of the coincidence of the two conditions is not surprising when one considers the incidence of carcinoma of the cardiac end of the stomach and of hiatus hernia, both of which are relatively uncommon. Actually, however, at the present

time hiatus hernia is diagnosed quite frequently, as noted above. Golden¹⁰ estimated that carcinoma of the cardiac portion comprised only 5% of all carcinoma of the stomach.

An extremely interesting case was reported by Holland and Logan¹². A 74 year old male was examined because of dysphagia and loss of weight. An X-ray examination demonstrated a hiatus hernia and an irregular outline in the lower esophagus. Esophagoscopy with biopsy was performed. The histological diagnosis was ulcerative esophagitis. A year later this was repeated and the histological report was grade 4 carcinoma. Jackson, who performed the esophagoscopies, commented that he had seen a few cases in which carcinoma developed in the herniated portion of the stomach but did not at all feel that the hiatus hernia was a causative factor.

Harrington¹⁷ who has published extensively on the surgical aspects of hiatus hernia, listed 5 of 223 patients operated on for hiatus hernia as having associated carcinoma of the stomach. No detailed information about these cases was given. In a recent article¹⁸ Olsen and Harrington reported 220 cases of patients with the shortened esophagus type of hiatus hernia. In three of these patients gastric carcinoma of the cardiac portion was demonstrated. Whether there is duplication of the cases in both papers mentioned by Harrington cannot be determined. Thus, all these cases are listed in Table 3.

Smithers¹⁹ presented the postmortem findings in the case of a 78 year old female who had a hiatus hernia and a carcinoma of the lesser curvature of the stomach. In the discussion of this paper, Dunhill mentioned that he knew of three and Johnstone was quoted as having seen 5 additional cases of carcinoma of the stomach together with a hiatus hernia of the shortened esophagus type. Smithers also reported another case of a 66 year old male with a hiatus hernia of the shortened esophagus type who had an adenocarcinoma of the cardia.

It will be noted that there is a total of 43 such cases of which only 23 were diagnosed either by necropsy, biopsy, or at surgery. Clinical diagnosis in all of the cases so listed, of course, includes roentgenologic examination. That X-ray examination may lead to an error in diagnosis, in this respect, is pointed out in two cases to be presented below. Two reports also indicated that a mistaken diagnosis of carcinoma of the stomach may be made in cases of hiatus hernia.

Rigerone²² in reviewing 12 cases of hiatus hernia reported a 60 year old female who had been vomiting three days. A mass the size of a grapefruit was felt in the epigastrium. Fluoroscopy showed complete obstruction at the pylorus and a diagnosis of gastric carcinoma was made. At operation, a hiatus hernia was found with most of the stomach being located above the

diaphragm. No carcinoma was noted. Huard²³ reported the case of a man who had had a gastric hemorrhage. The X-rays revealed a lesion in the antrum which was thought to be a carcinoma. At surgery, only a hiatus hernia was found to which the antral portion of the stomach had become attached.

In 24 of the 43 cases listed in Table 3 information as to the region of the stomach involved with neoplasm was given. Of these 24 cases, 13 or 54% occurred in the cardiac portion of the stomach. It is noted that several of this latter group were located in the herniated portion of the stomach. As previously noted, ordinarily only 5% of carcinomas of the stomach occur in the cardiac portion. In hiatus hernias, while the incidence of carcinoma of the stomach appears to be quite infrequent, when it does occur it is more frequently located in the cardiac portion of the stomach than is usually observed. It is realized that the number of cases is quite small and this impression is probably not statistically significant.

Case 1. B. C. H. #1093122. A 78 year old white female entered the hospital on April 11, 1945 complaining of vomiting of three weeks' duration. In 1942 the patient had an operation for a carcinoma of the hepatic flexure of the colon. She did well until ten months prior to admission when she began to lose weight. Three months prior to admission she started to have indigestion, characterized by epigastric pain and distress. For three weeks prior to admission, she had almost continuous vomiting with a great deal of gas and belching. Over the past nine months she had lost twenty pounds.

Physical examination revealed an emaciated female. There was a well healed right lower quadrant scar; a firm 3 x 1 inch mass was felt in the epigastrium and was thought to be liver edge.

Laboratory examination revealed a moderate hypochromic anemia and three guaiac negative stools. X-ray of the chest, pelvis, skull, and lumbosacral spine revealed no metastases. A barium enema revealed only diverticulosis of the descending colon. A gastrointestinal x-ray on April 23, 1945, revealed the esophagus to be short and the cardiac portion of the stomach in the chest. The stomach revealed a rather large filling defect involving the prepyloric portion. The defect was irregular, constant and no peristaltic waves passed through it. An ulcer crater was visualized in the center of the defect on the greater curvature side. In six hours there was a 5% residue in the stomach.

X-ray Diagnosis: 1. Shortened esophagus with a partial intrathoracic stomach. 2. Carcinoma, pyloric end of the stomach.

In view of the patient's condition, it was not felt that anything definitive could be done. She continued to vomit and had to be fed by stomach tube. The patient died on May 16, 1945.

Case 2. B. C. H. #1175559. A 79 year old white female was admitted on May 1, 1945, complaining of abdominal pain. Six weeks prior to admission the patient

began to experience burning pain in the epigastrium, which was partially relieved by amphogel. This was followed by vomiting which became progressively severe and frequent. Patient lost 16 pounds in six weeks. Fifteen years prior to entry, she had an operation, presumably gastroenterostomy, "for stomach ulcers". This operation was performed after many years of stomach trouble. Following this operation, she was placed on a diet and did fairly well until her present illness.

Laboratory findings revealed a "three plus" guaiac stool. Other laboratory results were not remarkable.

Physical findings were not remarkable.

Gastric analysis revealed no free acid before or after 0.5 cc. histamine subcutaneously. X-ray of the chest, lumbosacral spine and pelvis revealed no metastases. Gastrointestinal series on May 8, 1945, revealed a small hiatus hernia; an irregular filling defect was present in the pylorus causing obstruction. The stoma of a gastroenterostomy was seen to function and the duodenum filled only slightly. At the end of six hours 75% residue of the barium remained in the stomach. X-ray Diagnosis: Small hiatus hernia and carcinoma of the pylorus of the stomach.

On June 6, 1945, operation was performed. The lower third of the stomach was replaced by hard firm carcinoma; several metastases were noted in the liver and the lymph nodes on the lesser curvature of the stomach were enlarged. An anterior gastrojejunostomy was performed.

Patient did well for the first six weeks, but developed pneumonia with staphylococcus aureus bacteremia. She died on July 21, 1945.

Case 3. B. C. H. #1211887. A 78 year old white female was admitted on May 29, 1946, because of sudden swelling of the face. For three weeks prior to admission she had had nausea and vomiting. History was not very reliable.

Physical examination showed a large hard parotid swelling of the right side. Stensen's duct was reddened and showed exudation of pus on the right. Otherwise physical examination was not remarkable.

The patient's parotitis was treated and there was marked improvement in her condition. Further questioning revealed that patient had two episodes of pain in the right upper quadrant with jaundice. X-ray examination revealed a non-functioning gall bladder and multiple opaque calculi.

Because of complaints of epigastric distress after eating, a gastrointestinal series was obtained on June 27, 1946. This revealed a small hiatus hernia. A constant irregular narrowing of the prepyloric region was noted, but no ulcer was seen.

X-ray Diagnosis: 1. Early neoplasm of the prepyloric region. 2. Small hiatus hernia.

On July 22, 1946, the patient experienced left ventricular failure with pulmonary edema and despite treatment died on the next day.

Post-mortem examination revealed the stomach to be perfectly normal. Anatomical Diagnosis: Arteriosclerotic heart disease with congestive heart failure. Chronic cholecystitis with cholelithiasis. Biliary cirrhosis.

Case 4. B. C. H. #1248802. A 68 year old white male was first admitted to the hospital in 1941 because of epigastric pain and distress of two months duration.

Patient noticed that he had heartburn which was not influenced by eating, but seemed to be made worse by worrying and working. He was placed on a convalescent Sippy diet and there was some improvement. He was admitted on May 23, 1946, because of heartburn and cramping epigastric pain with little relationship to food. The patient was not very intelligent and history was not too clear. However, the same difficulty of gastrointestinal symptoms had been noted for six years, but had been getting progressively worse.

A gastrointestinal series on May 19, 1946, in the outpatient department revealed a large hiatus hernia. Immediately proximal to the pylorus there was an area of irregular narrowing with a penetrating ulcer extending off the lesser curvature side of the pylorus and measuring 1 cm. in diameter. There was some distension of the duodenal cap noted.

X-ray Diagnosis: 1. Large hiatus hernia. 2. Penetrating ulcer of the pyloric region. 3. Irregularity of the prepyloric region. 4. Malignancy cannot be ruled out.

On May 27 gastric analysis revealed 40 units of free HCl acid and 65 units after histamine. An operation was performed on June 5, 1947, at which time a penetrating ulcer adherent to the liver, 3 cm. above the pylorus, on the lesser curvature, was found. This had a benign appearance which was confirmed by microscopic examination.

A hiatus hernia admitting 3 fingers was also found.

A posterior gastroenterostomy was done because of the induration found at laparotomy. The patient withstood the operation well, but two weeks postoperatively he was still having the same symptoms he previously experienced.

It will be noted that in cases 3 and 4 carcinoma of the stomach was erroneously diagnosed in the presence of a hiatus hernia. In case 4, the error of diagnosing a benign lesion in the antrum for a malignancy is easily understood. But in case 3, no obvious explanation for the x-ray findings was forthcoming at necropsy.

CARCINOMA OF ESOPHAGUS ASSOCIATED WITH HIATUS HERNIA

In the present study only one of the 308 cases of hiatus hernia was associated with carcinoma of the esophagus. Unfortunately, data as to the incidence of this carcinoma in the 3448 patients studied was not obtained. However, in the age group in which the 308 hiatus hernias were found, it occurs not infrequently. Recently, Sweet²⁴ commented that carcinoma of the esophagus was a common disease occurring, in his experience, in two-thirds as many cases as carcinoma of the stomach.

The occurrence of esophageal carcinoma and hiatus hernia in the same patient is very uncommon. Moller⁴ in reviewing the literature was able to find only two cases. Wolf²⁵ reported a case, with necropsy confirmation of esophageal carcinoma in association with a hiatus hernia. Magnes²⁶ in discussing the short esophagus type of diaphragmatic hernia stated that he had seen three cases of concurrent esophageal carcinoma. Raven²⁷ reported the occurrence of a carcinoma of the esophagus in a 58 year old male

who had a shortened esophagus type of hiatus hernia. Harrington¹⁷ mentioned operating on three patients who had esophageal carcinoma and hiatus hernia. Olsen and Harrington¹⁸ presented another case of an esophageal carcinoma proved by biopsy with a hiatus hernia. In the paper by Smithers¹⁹ mention is made of a 48 year old male with a hiatus hernia who had an epidermoid carcinoma of the esophagus. Thus, in all, twelve cases of this combination have been previously recorded. Summary of the thirteenth such case is given.

Case 5. B. C. H. #1195716. A 61 year old colored male was admitted on December 4, 1945, because of hemoptysis and dysphagia. Eight months prior to admission, the patient noted pain to the left of the midline in the substernal region on attempting to swallow meat or solid foods. Liquids could be swallowed with ease and there was not much progression of the dysphagia. He was hospitalized six months previously because of pain in the right chest, chills, fever, and hemoptysis. There was a great deal of coughing, and the pain was pleuritic. The entire right lung was the site of a pneumonic process associated with a type 4 pneumococcus bacteremia and types 4 and 22 pneumococci in the sputum. There was clearing on sulfadiazine, but a residual area in the right apex remained. Two sputum examinations and a guinea pig study were negative for tuberculosis, but the patient refused to stay for further study and signed out against advice 24 days after admission. Shortly after leaving the hospital, he had expectoration of blood and dysphagia returned. A gastrointestinal series was done in the out-patient department four months prior to admission and was reported to be negative. The night before admission, the patient had a coughing spell and thereafter brought up 1½ quarts of liquid which was brown in color.

Physical examination was not remarkable.

Aside from 2 stools that showed a "one plus" guaiac test, laboratory findings were not remarkable. X-ray of the chest showed a mottled infiltration in the right upper lung field with no cavitation, consistent with pulmonary tuberculosis. A gastrointestinal series on December 20, 1945, revealed an irregular constricting lesion 4 cm. in length in the mid-esophagus. A small hiatus hernia was also present.

The patient was transferred to a surgical service and biopsy was performed. The biopsy of the lesion in the esophagus revealed epidermoid carcinoma. An operation was performed on January 30, 1946, and esophagotomy and esophagogastrostomy was performed. The carcinoma of the lower middle-third was removed, as were some metastatic para-aortic nodes.

On the 8th post-operative day the anastomosis came apart. Two days later the patient died of a terminal mediastinitis.

DISCUSSION

In 308 cases of hiatus hernia, there were two associated carcinomas of the stomach and one of the esophagus. On the basis of the occurrence of carcinoma of the stomach in 2.92% of the total cases studied, and because of

the age groups concerned—80% of the patients with hiatus hernia were over 50 years old—it was thought to be of value to review this association. In this study, the chances of a patient with a hiatus hernia having a carcinoma of the stomach were four times less than in patients without a hiatus hernia. This, clinically, seems analogous to the impression that the presence of a duodenal ulcer in a patient affords some protection against the occurrence of carcinoma of the stomach. There does not seem to be any logical explanation for the lessened frequency of carcinoma of the stomach in patients with hiatus hernia. On purely speculative grounds, one might imagine that the increased “irritation” that the herniated part of the stomach in a hiatus hernia is subjected to, might cause an increase in gastritis and possibly carcinoma in this portion of the stomach. That this does not occur is obvious. This does not lend any support to the theories of some authors who feel that continued trauma or foci of irritation, or repeated small insults may lead to carcinoma. There does, however, seem to be a greater incidence of carcinoma in the cardiac portion of the stomach in patients with hiatus hernia than is usually found. Whether or not this is significant cannot be stated at present.

SUMMARY

1. The association of hiatus hernia and carcinoma of the stomach and esophagus is reviewed.

2. In this group of 308 cases of hiatus hernia, carcinoma of the stomach occurred in 0.65%, while it was present in 2.92% of all the patients studied. In half of the cases in which carcinoma and hiatus hernia were found together, the carcinoma was in the cardiac portion of the stomach.

3. Carcinoma of the stomach may be erroneously diagnosed in cases of hiatus hernia by roentgen study.

4. Carcinoma of the esophagus occurs infrequently in patients with hiatus hernia.

5. Two cases of carcinoma of the stomach and one of carcinoma of the esophagus, in association with hiatus hernia, are added to the small number of previously recorded cases.

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FLUID IN THE LESSER OMENTAL SAC AS A CAUSE OF EXTRA-GASTRIC PRESSURE DEFECT

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The differential diagnosis of the cause of pressure deformity of the stomach due to adjacent structures has been limited in most text-books to disease of the organs in anatomic relation with the stomach. Anteriorly, the stomach is in contact with the left lobe of the liver on the right, with the diaphragm and anterior body wall on the left. The pylorus reaches the quadrate lobe of the liver. Posteriorly, it is separated from the pancreas by the lesser omental sac; below, with the transverse mesocolon, and through this, with the transverse colon and coils of small intestine.

Since the stomach is fixed at two points, the cardiac and pyloric ends, by ligaments, any displacement from behind would force it anteriorly and rotate it to the right. Such displacement is frequently suggestive of enlargement of the body or tail of the pancreas. It is more difficult to explain pressure exerted on the lesser curvature. Roentgenologists report with moderate frequency a smooth rounded mass which pushes the stomach downward and to the left, and have ascribed this either to an enlarged left lobe of the liver, or to an unidentifiable mass. If at operation or autopsy no such mass is found, the x-ray finding is promptly forgotten.

We have recently seen 2 cases in which x-rays suggested a mass displacing the stomach and causing indentation on the lesser curvature. The cause, in both cases, was a collection of fluid in the lesser omental sac, resulting probably from partial or complete sealing of the foramen of Winslow by inflammatory exudate.

Case #1. M. R., male, age 58, was admitted to the hospital twice in 2 years for chills, fever, and abdominal pain. On the first admission, in 1946, the liver was enlarged and right lower lung atelectasis was noted. The blood showed a leukocytosis and culture was positive for staphylococcus aureus. Recovery followed therapy with penicillin. On re-admission in January 1948 he was found to have icterus, an enlarged liver, palpable spleen, and signs of consolidation in the right lower lung. A mass was noted in the right upper flank region, oval in shape. Stools were tarry. X-ray revealed an elevated diaphragm on the right and a mass which pushed the stomach anteriorly.

Necropsy revealed 2000 cc. of purulent fluid in the abdomen, and a fibrinous granular substance covered the parietal and visceral peritoneum. The liver was adherent to the gastro-hepatic omentum and was studded with multiple abscesses. The sigmoid colon was surrounded by a thick mass which covered a perforated di-

verticulum. No masses were found which impinged on the lesser curvature of the stomach, but a large amount of fluid was released from the lesser omental sac.

This patient died of multiple liver abscesses originating from a ruptured diverticular abscess with peritonitis. The X-ray finding of extra-gastric mass could be explained only by the fluid-filled lesser sac.

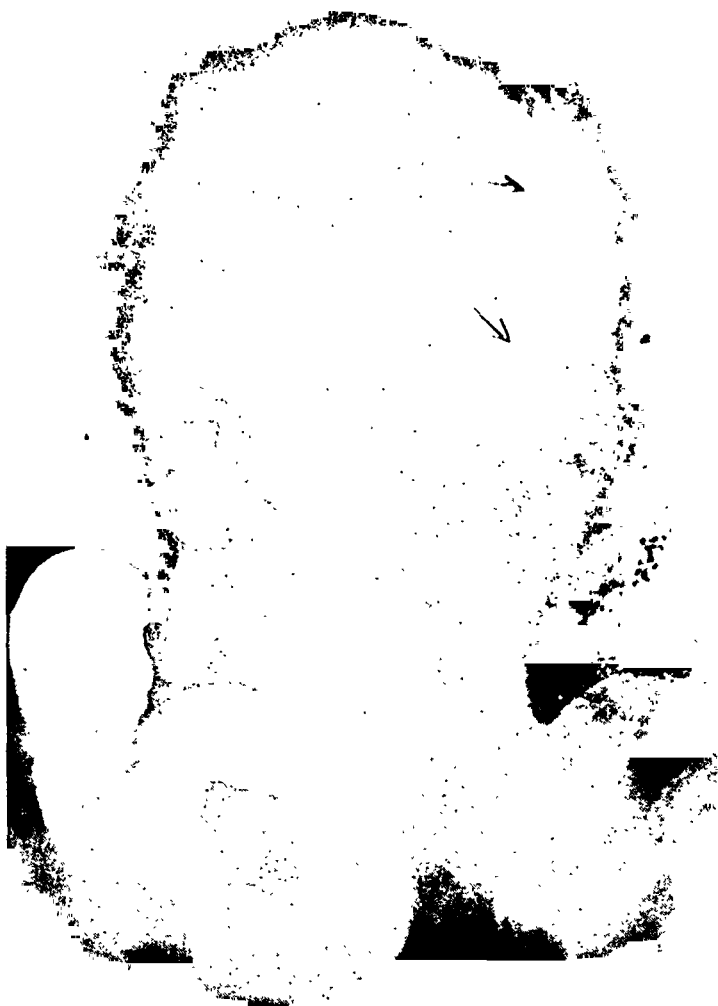


FIG. 1. Case #2. M. S.

Case #2. M. S., female, age 62, suffered an acute attack of pain in the right upper quadrant of the abdomen, accompanied by nausea and anorexia. The pain persisted for 3 weeks with low grade fever. The clinical picture indicated acute cholecystitis with possible empyema of the gall bladder. The abdomen was somewhat spastic in the right upper quadrant, but the sensation of a rounded mass was

obtained in the epigastrium. X-rays revealed calculi in the gall bladder, and in addition, a mass which produced a rounding and displacement of the lesser curvature of the stomach. (Figures 1 and 2)

At operation, the gallbladder was gangrenous but intact, and contained numerous calculi. Careful insertion of the finger into the foramen of Winslow resulted in a

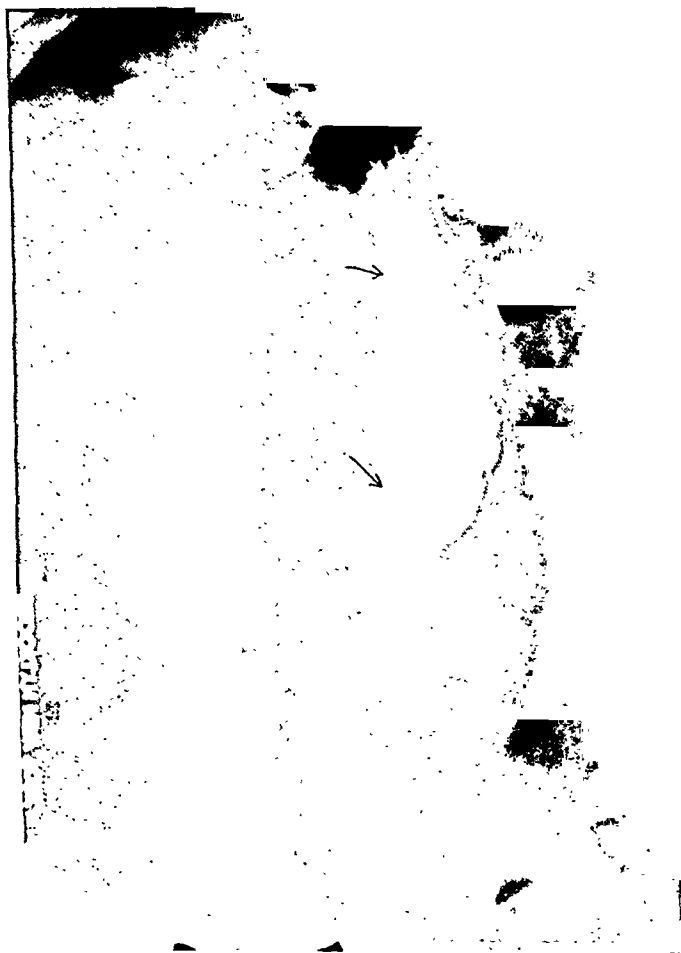


FIG. 2. Case #2. M. S.

gush of clear serous fluid from the lesser sac. No other masses or pathology were found in the abdomen.

This patient also showed solely a fluid-filled lesser omental sac to account for the x-ray findings. The cause might easily have been overlooked had not curiosity prompted probing of the foramen.

COMMENT

The lesser omental sac is formed by reflections of peritoneum extending from the lesser gastric curvature to the under surface of the liver. While it is possible for the sac to remain patent in the greater omentum as well, this portion is usually sealed, so that the open space lies above and partly behind the stomach. The only communication existing with the greater sac or peritoneal cavity is the foramen of Winslow, which is relatively small and admits one to two fingers. Baylin and Weeks¹ report that in acute pancreatitis the foramen may become sealed off, isolating the lesser sac where large collections of fluid may displace the stomach. Grayish membranous exudate covered the opening in their cases, and a necrotic pancreas was found at the border of the sac. It is conceivable that any inflammatory process in the region of the foramen could produce enough exudate to fill the lesser sac and form a membrane over the opening. Acute cholecystitis might be found to produce such a phenomenon if the surgeon would observe whether free fluid escapes when he inserts his finger into the foramen. Similar observation by the pathologist during necropsy might also add to the statistics, and could provide a simple explanation for an oft-times puzzling roentgenologic finding.

CONCLUSIONS

1. Two cases are presented in which x-rays revealed a mass causing smooth indentation of the lesser gastric curvature and displacement of the stomach.
2. In both cases, a fluid-filled lesser omental sac was found, with no other visible cause for the gastric defect.
3. It is suggested that the lesser omental sac be carefully scrutinized by surgeons and pathologists in those cases in which x-ray indicated an extra-gastric mass of this nature. More frequent observation might provide an explanation for a frequently puzzling roentgen finding.

Note: Case #1 is presented with the permission and through the courtesy of Dr. C. G. Burn, pathologist, Kings County Hospital.

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THE GASTRIC DISTENTION TEST IN CHRONIC GASTRITIS

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DIAGNOSIS OF GASTRITIS

Gastroscopy is the best method for diagnosing gastritis. By this method the diagnosis of chronic gastritis can usually be made without ambiguity, although very fine changes may be overlooked. The correlation of gastroscopic and microscopic findings is surprisingly good.

Physical examination does not show anything typical and the symptoms are inconsistent. (Consult for this and the following considerations the monograph of one of us (R. S.) on "Gastritis".)¹ X-ray examination of the stomach only rarely makes the diagnosis of gastritis. All signs described have been found to be misleading and disappointing. Sometimes, but not often, tenderness over the silhouette of a barium filled stomach may suggest superficial gastritis. The nodular appearance of the relief picture ("corn-cob"-relief picture) described by Berg is demonstrable only in very few of the most severe cases of atrophic-hyperplastic and of hypertrophic gastritis. An increase in the thickness of the folds in hypertrophic gastritis can, on the whole, not be considered to be a reliable sign; it may even be present in atrophic gastritis and in normal stomachs. Templeton² believes that folds broader than 1 centimeter are evidence of gastritis. Stiffness of folds, indicating inflammatory involvement of the submucosa (Templeton), is rare. Templeton described the occasional occurrence of "cross-hatching" of the folds as sometimes equivalent with the gastroscopic "beady" appearance of inflamed folds. Apparent thinness of the folds at x-ray examination cannot be considered as a sign of atrophic gastritis (Ansprenger and Kirklin,³ Templeton). The demonstration of gastritic ulcerations was tried without significant success by Schindler and Sielman⁴, Henning⁵, Ansprenger and Kirklin. Thus, x-ray examination does not make the diagnosis in the great majority of all cases of gastritis.

Gastric analysis contributes but little to the diagnosis of gastritis. It is true that histamine-proved anacidity occurs frequently in either superficial or atrophic gastritis, but since anacidity without gastritis occurs (Carey⁶) and anacidity is often not found in gastritis, gastroscopic confirmation is still necessary.

Cytodiagnosis, the study of the number and kind of cells in the gastric contents, was developed especially by Mulrooney and Eusterman⁷. It may permit the differential diagnosis of psychoneurosis and gastritis. However, it rarely permits the distinct diagnosis of gastritis.

THE DISTENTION TEST*

Henning recognized the desirability of developing methods which would permit the diagnosis of gastritis without gastroscopy. Of the several methods he devised, the distention test appeared the most promising and interesting one. It was described first in a paper by Henning and Norpoth⁸; its principle is the provocation of distention pain. The authors used the test in twenty-seven patients and deemed it important in the diagnosis of gastritis.

Because of the simplicity of the test we decided to check their studies, and this paper is a report on that study. Our series of 32 cases consisted of patients with normal stomachs, and of patients with gastritis, and some associated diseases. The test was avoided in patients with ulcerations of the stomach, as we were afraid of perforations as a consequence of the distention; yet the series contains two ulcer patients. In order to avoid any bias, care was taken that the performer of the test did not know the gastroscopic diagnosis beforehand.

The principle of the distention test is simple. It answers the question of whether or not pain is felt if the gastric wall is distended with a certain amount of air. After consideration of the vast literature Henning⁵ came to the conclusion, that "two types of gastric pain must be differentiated, the hunger pain—often considered as a phenomenon of motility—and the early pain, being connected with the distention of the stomach." Gastroscopic observations had led him to the conclusion that the pain of patients suffering from gastritis may be a distention pain.

METHOD

The following technic was used for studying this distention pain.

For the distention of the stomach, air is inflated through a rubber tube directly into the stomach.

Henning and Norpoth⁸ found that this direct inflation is preferable to the use of a dilating balloon. They felt that the irregularly shaped stomach is unevenly distended by a balloon; some portion may be distended too much, while others, perhaps the seat of patchy gastritis, might not be distended at all. They thought furthermore that use of the balloon would add to the mere distention an undesirable element of friction. The obvious disadvantage

*No discussion of the theoretical foundation of the distention pain will be undertaken in this paper.

of air inflation, that air might escape from the stomach into the intestine, could be circumvented easily as will be shown later.

We replaced the original Ewald tube by a Levine tube which is less disagreeable to the patient. The patient swallows the tube. When it has reached the stomach, suction is applied and the stomach is completely emptied. Then the proximal end of the Levine tube is connected to one end of a T rubber tube. The second end of the T tube is attached to an inflating balloon and its last end is connected with a water manometer.

The patient then lies on his back in a comfortable position. Belt and collar must be loose. The patient then is instructed to breathe quietly, to lift one of his hands as soon as he feels any distress, however to hold as much air as possible. Bloating or feeling of distention should not be a reason to give the signal, unless he feels that he would have to belch if more air were injected. The communication between manometer and inflating balloon then is closed and the inflation of air into the stomach is started. It must be done slowly. When the patient gives the signal agreed upon the communication between the Levine tube and manometer is established and the manometric pressure is read. During the observation of the pressure care is taken to listen at the duodenal region, in order to recognize the escape of air from the stomach into the duodenum. A characteristic noise then is heard; and at the same time the manometric pressure drops suddenly, in a manner quite different from oscillations caused by gastric spasms. Then some more air has to be inflated until the maximum tolerance point of the patient is reached again. The whole procedure takes about five to fifteen minutes.

RESULTS

See Table 1. There were eleven patients who experienced no pain at the distention test. Five of them had a normal stomach at gastroscopic examination. These five patients were sensitive psychoneurotics, yet they were able to tolerate a manometric pressure of 8.5 centimeters of water or more. (These figures are not comparable to the figures of Henning and Norpoth who used a different type of tube.) Three patients who felt no pain at the time of the distention test, suffered from atrophic gastritis. In these the spontaneous distress had much improved at the time the distention test was undertaken. Two patients without pain at the distention test had hypertrophic gastritis. In one of them the spontaneous distress had much improved at the time the distention test was done. There was furthermore one patient with marked superficial-atrophic gastritis with rather severe distress at the time of the test, who nevertheless did not experience any pain when the stomach was distended. In four of these pathologic stomachs without distention pain, the tolerance

TABLE 1
Results of distention tests in thirty-two patients

GASTROSCOPIC DIAGNOSIS	CASE NO.	TOLERANCE FOR AIR (MANO- METRIC PRESSURE EXPRESSED IN CENTI- METERS OF WATER)	NO PAIN	PAIN		REMARKS
				Differ- ent from	Imi- tating	
Normal stomach (6 cases)	1	10	+			
	2	11	+			
	3	8.5	+			
	4	10	+			
	10	9	+			
	30	7		+		
Ulcer						
Duodenal	13	6			+	Plus gastric purpura
Gastric	22	5			+	Plus atrophic gastritis
Chronic superficial gastritis (5 cases)	12	5			+	
	14	6.5			+	
	26	6.5			+	
	29	6			+	
	32	7			+	
Chronic atrophic gastritis (11 cases)	19	5			+	
	20	7.5			+	
	21	7.5			+	Plus benign polyp
	23	7.5			+	
	24	7			+	
	25	5.5			+	
	27	5			+	After superficial gastritis
	28	5		+		Plus cholecystitis
	8	8	+			Distress improved at time of dis- tention test
	9	5.5	+			Distress improved at time of dis- tention test
	11	6.5	+			Distress improved at time of dis- tention test
Hypertrophic gas- tritis (5 cases)	6	11	+			Distress decreased at time of dis- tention test
	7	8	+			Plus cholelithiasis
	16	5.5			+	
	17	6-12.5 (not too certain)			+	
	18	6.5			+	
Superficial plus atrophic gastritis (2 cases)	5	8	+			Had severe distress at time of test
	31	7		?	?	
Superficial plus hypertrophic	15	4.5			+	

for air inflation was at a manometric pressure of 8 or more centimeters of water. In two cases the tolerance was only 5.5 and 6.5 centimeters of water.

Twenty-one patients experienced pain at distention. Only one of them had a normal stomach gastroscoically. The observer had the impression that in this case the pain with irradiation into the back was due to the dilatation of a loop of small bowel. Yet, this case reveals that pain of a distention test does not necessarily prove the presence of organic disease of the stomach.

As previously mentioned only two cases of ulcer were tested. One case of duodenal ulcer was accompanied by gastric purpura, one case of gastric ulcer was complicated by atrophic gastritis. In both cases inflation of small amounts of air (5 and 6 centimeters of pressure) produced the same pain from which the patients were suffering spontaneously.

All five patients with pure superficial gastritis experienced pain at the distention test. This pain was usually described as dull epigastric pain. In all cases it imitated exactly the spontaneous pain for which the patients had consulted us. (It must not be forgotten that one case of marked superficial-atrophic gastritis felt no pain at the distention test.)

Of the eleven cases of pure atrophic gastritis, eight experienced pain when the stomach was distended. In seven of them this pain imitated their spontaneous pain. In one there was a difference: the patient suffered spontaneously from pain located below the right costal margin, due to a chronic cholecystitis the existence of which was proved by biliary drainage; at the time of the distention test she felt very slight epigastric pain.

Of the five patients with hypertrophic gastritis, three experienced pain at distention identical with their spontaneous pain. In one case of superficial plus atrophic gastritis there was pain at distention, but the patient could not state with certainty whether or not the pain was identical with the spontaneous distress.

Superficial gastritis is rarely found together with hypertrophic gastritis. Yet there was one case in our material, in which exceedingly severe superficial gastritis was seen to overlap hypertrophic swelling of the mucosa. This patient had the lowest tolerance for distention—only 4.5 centimeters of water pressure. He experienced dull epigastric pain on distention and this pain was identical with the pain which had forced him to seek medical aid.

It is not possible to explain why some patients with chronic gastritis do not respond to distention of the stomach with pain, while the majority do. A lowered pain threshold should be considered. We know how much the microscopic pictures of chronic gastritis vary, extensive inflammatory edema being present in some cases of atrophic gastritis and absent in others. The fact that so many patients having superficial gastritis experienced pain when their stomachs were distended seems important. Mucosal edema is the chief

histopathologic sign of chronic superficial gastritis. One may speculate that pain during the distention test may be due to the presence of edema. However, in one case of marked superficial-atrophic gastritis no pain was present.

CONCLUSIONS AND SUMMARY

1. If pain is experienced when the stomach is distended with air, organic disease of the stomach is likely to be present. Yet pain may occasionally be felt by patients with normal stomachs.

2. If pain experienced when the stomach is distended with air imitates the patient's spontaneous pain, and if gastric and duodenal ulcer can be excluded, some kind of gastritis is likely to be present.

3. The distention test does not permit differentiation of the different types of gastritis. There are cases of chronic gastritis, in which no pain is felt at the distention test. Therefore, the distention test cannot replace gastroscopy in the diagnosis of gastritis.

4. The rather regular occurrence of distention pain in cases in which at gastroscopy pure superficial gastritis was seen, and the identity of this pain with the spontaneous pain of the patients, seems to prove that chronic superficial gastritis is a definite pain producing disease entity.

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Case Reports

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PRIMARY SYSTEMIC AMYLOIDOSIS WITH JAUNDICE AND HEMORRHAGE

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Amyloid disease may be subdivided into three main groups:

1. Primary amyloidosis.
2. Secondary amyloidosis.
 - a. Associated with tuberculosis or chronic suppuration.
 - b. Associated with multiple myeloma.
3. Localized amyloidosis.

Primary amyloidosis is characterized by an absence of known etiologic factors. The amyloid is found in smooth and skeletal muscle, the cardiovascular system and the gastrointestinal tract; while the organs usually affected in secondary amyloidosis, such as liver and spleen, are uninvolved.

Secondary amyloidosis of the ordinary type usually follows longstanding disease such as tuberculosis or chronic suppuration. The liver, spleen, kidneys, and adrenals are characteristically involved and the amyloid is deposited beneath the endothelium of capillaries and arterioles. In the type associated with multiple myeloma, on the other hand, the distribution is characteristically that of primary amyloidosis.

It has been stressed that overlapping of characteristics and atypical distribution can occur.¹ Consequently, primary amyloid disease may involve chiefly, the liver, spleen, and adrenals; whereas, secondary amyloid disease may cause infiltration of mesodermal tissues.

In 1948 Lindsay² referred to 48 cases of primary systemic amyloidosis recorded in the literature and added 1 case of his own. Because of the rarity of this disease and the diverse clinical picture which it presents, a correct ante mortem diagnosis has seldom been made. The cases usually diagnosed ante mortem have been those in the group associated with *macroglossia*, in which event a biopsy of the tongue has established the correct etiology, or associated with cutaneous involvement in which event skin biopsy has

clarified the diagnosis. These cases apparently belong to a group characterized by involvement of the heart, tongue, and skin. Liver biopsy has permitted the diagnosis of primary amyloidosis in two cases previously studied³ in this hospital. Liver biopsy therefore presents a method of accurately establishing the diagnosis of primary amyloidosis ante mortem although a review of the literature fails to reveal its employment for this purpose. The procedure was not attempted in the instance now under consideration because of the critical nature of the patient's illness at all times following his admission to the University Hospital.

The following case of primary systemic amyloidosis is being reported because of two features, jaundice and massive hemorrhage, neither of which is commonly associated with the disease.

CASE REPORT

J. K., U.M., #784782. The patient was a 68 year old white farmer who was admitted to the Medical Service of the University of Minnesota Hospitals on December 15, 1947, and expired on January 12, 1948.

He had been weak and irritable for 7 months prior to admission, and for the same period of time had noted a hard mass in the right upper quadrant of the abdomen, which had gradually increased in size. Five weeks prior to admission, the patient awoke to find that he was bleeding from the nose and gums. Examination by a local physician revealed rectal bleeding also. In spite of packing and cauterization, bleeding continued intermittently until the time of this admission and he had already received 12 blood transfusions in his local hospital. There was no history of familial bleeding or of previous bleeding episodes. He had always been in good health, and denied excessive use of alcohol or exposure to drugs or toxic agents.

Physical examination at the time of admission revealed a temperature of 99 degrees F., pulse rate of 108 per minute, respiratory rate of 20 per minute, and blood pressure of 158/90. The patient was well-developed, well-nourished, and moderately pale. There was slow oozing of blood from the nose and gums, but the tongue appeared normal. The heart was demonstrably enlarged, and a harsh systolic murmur was heard over the entire precordium. The liver was palpable 5 cm. below the costal margin in the mid-clavicular line. The spleen was questionably palpable on admission, but could not be felt thereafter. There were numerous large ecchymoses over the entire body with a massive hematoma of the right shoulder and arm (Fig. 1). A single hemorrhage was seen in the fundus of the right eye. There was a grade one pitting edema of the ankles.

Laboratory investigation revealed the urine to be normal. The hemoglobin was 6.2 grams, the erythrocyte count 2,230,000, leucocyte count 13,400, with 74% neutrophils, 14% lymphocytes, 2% monocytes, 9% eosinophiles, and 1% basophiles. Repeated leucocyte counts showed little variation, and the eosinophile percentage remained below 4%. Bleeding and clotting times, clot retractility study, and platelet counts were repeatedly carried out and were within normal limits at all times.

Repeated cuff tests were negative, except on one occasion when 20 petechiae were found in a 5 cm. circle. Erythrocyte fragility was normal. Numerous prothrombin times ranged from 36.4 seconds with a control of 12.6 seconds to 27 seconds with a control of 15 seconds, corresponding roughly to 12 to 37%. The serology was negative. The stools were persistently tarry, and showed a 4 plus benzidine and guaiac test. Blood urea nitrogen ranged from 11 to 31 mg. per cent. Plasma proteins were 6.7 grams per cent, of which albumin was 3.6 grams per cent, globulin was 2.7 grams per cent, and fibrinogen was 0.4 grams per cent. Blood cultures were sterile. Liver function studies on admission showed a 1' (prompt direct) bilirubin of 0.8 mg. per cent, with a total of 2.4 mg. per cent. Thymol turbidity was 9.3 units, cephalin-cholesterol flocculation was 0 at both 24 and 48 hours. The alkaline



FIG. 1. Hematoma of right shoulder and large ecchymoses

phosphatase was 3.6 Bodansky units, the total cholesterol was 226 mg. per cent, with 130 mg. or 58% of the total representing the esterified portion. Urine urobilinogen was 6.6 mg. per 24 hours; feces urobilinogen was 700 Ehrlich units per 100 grams. Urinary coproporphyrin was 591 gamma per 24 hours, of which 87% was Type I isomer.

X-ray examination of the chest showed only slight cardiac enlargement of the left ventricular type. X-ray of the right shoulder was negative. Two sternal bone marrow biopsies were considered to be compatible with blood loss and gave no evidence of multiple myeloma.

During the patient's hospital stay he had a continuous fever of about 100 degrees F. He bled profusely from the gums, nose and rectum, and numerous large ecchymoses appeared on his trunk and extremities. He received 5 liters of blood which

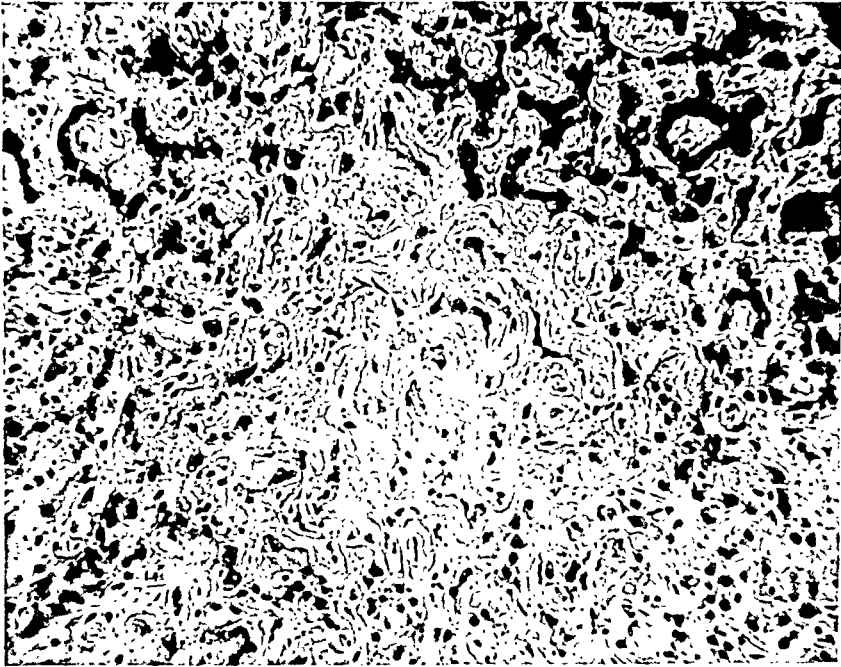


FIG. 2. Histologic section of liver showing replacement by amyloid stained with hematoxylin and eosin.

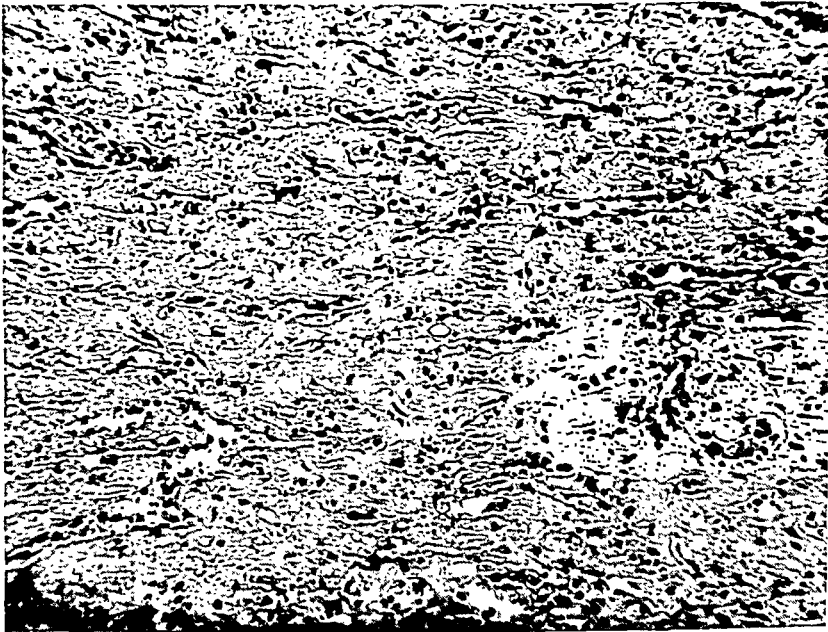


FIG. 3. Histologic section of spleen showing replacement by amyloid stained with hematoxylin and eosin.

maintained his hemoglobin between 6 and 7 grams. 72 mg. of Vitamin K. given intravenously shortly after admission had no effect on the prothrombin time, whereas 500 cc. of fresh plasma lowered it from 34.6 seconds to 27.5 seconds (control 14.4

seconds). He was fed a high carbohydrate, high protein, high calorie diet, and received 12 mg. of Vitamin K. and 500 mg. of Vitamin C. daily. The patient became visibly jaundiced, and the liver function studies done at intervals showed increasing functional impairment. Values obtained several days prior to death showed a 1' serum bilirubin of 2.0 mg. per cent with a total of 4.6 mg. per cent. Thymol turbidity was 15.9 units, cephalin flocculation one plus at 48 hours, alkaline phosphatase 10.5 Bodansky units, and total cholesterol 208 mg. per cent, of which 99 mg. were esters. Fractional protein was 6 grams per cent, of which albumin was 2.8 and globulin 3.2.

On January the twelfth the patient suddenly became comatose, with accompanying shock. Neither neck rigidity nor other localizing neurological signs appeared, and death occurred without return of consciousness.

*Necropsy Findings**

The heart weighed 550 grams, with normal valves and hypertrophied myocardium. The spleen weighed 950 grams. The surface was firm and smooth, and appeared somewhat pale. The cut surface bulged and was pale, meaty, and very firm. The liver weighed 3250 grams. The surface was smooth and the margin was rounded. The cut surface bulged, was pale, yellowish-brown in color, and had a slightly waxy appearance. Examination of the gastrointestinal tract showed no gross hemorrhage, ulcer or esophageal varices. The brain showed a small amount of subarchnoid hemorrhage over the hemispheres, and there was some clotted blood in the middle cranial fossa, and above the tentorium especially on the right. There was also some blood around the base of the brain. Microscopic examination showed the liver cords to be markedly atrophic and narrowed. Between the liver cords there was a large amount of amyloid (Fig. 2). The spleen was almost completely replaced by amyloid so that the normal architecture could not be made out (Fig. 3). Small amounts of amyloid were seen in the myocardium, around blood vessels, in the kidneys, and traces were found in the esophagus and gums. Marrow taken from the ribs showed no evidence of multiple myeloma. No amyloid was seen in the brain, or in any organ other than those mentioned.

COMMENT

In 1936, Moschcowitz⁴ stated that jaundice never occurred in amyloidosis. Tiber, Pearlman, and Cohen⁶ studied 30 cases of secondary amyloidosis and found liver function tests to be normal in all of them. Five cases of jaundice have been reported associated with amyloidosis.⁵⁻⁹ The etiology of the jaundice is not clear, since extensive involvement of the liver often occurs without jaundice being present. The unusual jaundice of amyloidosis has been attributed to extensive infiltration of the liver with consequent destruction of parenchymal and reticulo-endothelial cells; to obstruction of bile canaliculi; or to associated cirrhosis. However, the exact etiology of the

*Necropsy performed by Dr. C. W. Freeman of the Department of pathology, University of Minnesota.

jaundice is not known, and more than one of the factors just mentioned may play a role.

Purpura, hematemesis, melena and hematuria have been described in amyloidosis and have been attributed to vascular infiltration with amyloid. However, the degree of hemorrhage seen in this case has seldom been reported. Extensive hemorrhage occurred in three cases studied by Lubarsch¹⁰, Dillon and Evans¹¹, and Pearson et al¹², each reporting one of the three; but in none of these patients were both jaundice and hemorrhage present simultaneously. Investigation of the clotting mechanism revealed only a prolonged prothrombin time in one case¹¹. In our patient, a prolonged prothrombin time was the only abnormality in the clotting mechanism that could be detected. Whether or not this could account for the extensive hemorrhage is difficult to say, since many patients receiving anticoagulant therapy have a prothrombin time in the same range without gross hemorrhage. Vascular infiltration with amyloid might explain the bleeding, yet one would expect a positive cuff test were this the case.

SUMMARY

A case of primary systemic amyloidosis is reported with principal involvement of the liver and spleen and with resultant jaundice, hypoprothrombinemia, and extensive hemorrhage. None of these features are usually associated with primary amyloidosis, and their coexistence is of unusual rarity. The etiology of the amyloidosis in this case is unknown, as is also the exact basis for the unusual manifestations.

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THE CONTROL OF ESOPHAGEAL HEMORRHAGE BY PNEUMATIC TAMPONADE AND THROMBIN

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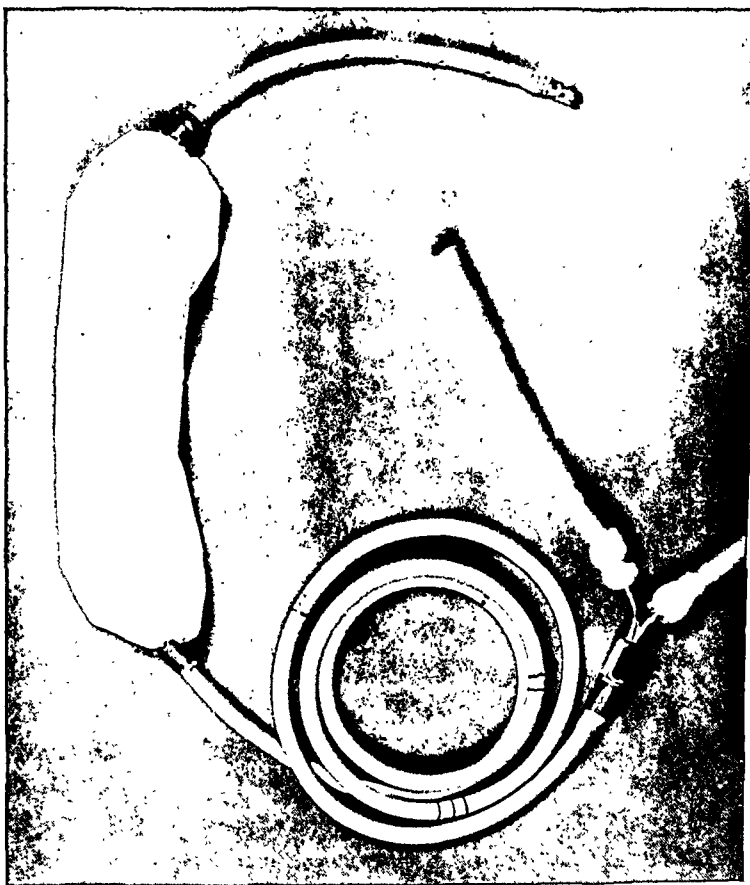
When the symptoms and signs of portal hypertension are present in a person suffering from hematemesis or melena, it may be assumed that an esophageal vessel has ruptured. Hemorrhage from esophageal varices may be massive producing exsanguination and shock that demand emergency treatment. Schiff¹ in an analysis found this disease to account for 10% of a group of patients with alimentary bleeding. Until quite recently the only means of therapy were supportive. Tocantins² described a pneumatic tamponade which, when distended in the cardiac portion of the esophagus permitted sufficient compression of the varices to control bleeding. Shortly thereafter Rowntree and his associates³ reported the use of a modified apparatus with a more elongated balloon permitting pressure over a larger area of the distal esophagus. The purpose of this communication is to describe the application of such a tamponade with an additional refinement in technique.

The apparatus is adapted from a Miller-Abbott tube cut to a length of sixty centimeters. Near the distal end a latex balloon, fifteen centimeters in length, is secured about the tube so that the openings of one lumen will permit inflation. Beyond the balloon the tube extends for fifteen centimeters and contains openings from the opposing lumen. This allows aspiration of, and injection into the stomach when the tamponade is distended in the esophagus. When the balloon is inflated within the esophagus, it compresses the varices sufficiently to interrupt bleeding.

Additional coagulation can be induced in the ruptured vessel by the local application of a thrombin preparation, as suggested by the report of Daly⁴ who employed a buffered thrombin mixture successfully in bleeding peptic ulcer. For esophageal hemorrhage, the tamponade is inflated and coated with Topical Thrombin (Parke-Davis Co.) and again collapsed before it is introduced. The apparatus is then inserted to the correct position in the esophagus and the balloon is distended with approximately 180 cubic centimeters of air. Following this the patient is given by mouth, at thirty minute intervals, five cubic centimeters of a 1:10 solution of Topical Thrombin for a total of four doses. This solution seeps down around the tamponade and provides additional hemostasis in areas where oozing continues. The following case reports illustrate the clinical application of the esophageal tamponade:

B. C., a 15 year old white boy, was admitted to the Barnes Hospital, November 13, 1947, complaining of massive hematemesis. The admission history revealed the

onset of diabetes mellitus and discovery of an enlarged spleen and liver 11 years previously. In 1940, a diagnosis of Banti's disease was recorded on the basis of hepatomegaly, splenomegaly, anemia, and leukopenia. Because of these findings, a splenectomy was performed on October 17, 1940. In July 1944, he had the first of seven severe episodes of hematemesis occurring over the next $3\frac{1}{2}$ years. A gastrointestinal x-ray study in March 1947, revealed esophageal varices in the distal half of the esophagus. He had had two episodes of diabetic coma in the past.



Photograph of pneumatic tamponade on a double lumen tube.

The present attack began one day prior to admission with syncope followed by nausea and epigastric pain. Six hours before admission, he vomited "two quarts" of bright red blood and again fainted. There were two smaller hematemeses three hours and one hour before entry, and on arrival he again vomited 500 cc. of bright red blood. He had taken nothing by mouth for 18 hours and had taken no insulin on the day of admission.

Physical examination revealed the pulse to be 152 per minute and the blood pressure 70/0 mm. of Hg. He was restless and complaining of thirst and nausea. The skin and mucous membranes were pale and dry. The liver was not palpable.

Admission laboratory data revealed 3,050,000 red blood cells, 7.5 gm. hemoglobin,

hematocrit 24%, and 18,400 white blood cells. The stool was tarry and had a strongly positive guaiac reaction. There was 4 plus glycosuria and 4 plus acetonuria. The blood non-protein nitrogen was 42 mg%, blood sugar 382 mg%, CO₂ combining power 22.1 mEq., and plasma chloride 95 mEq. His prothrombin time was normal.

Transfusion of whole blood was begun as soon as possible and a total of 1,500 cc. was given over the course of the first 12 hours with rapid recovery from shock. Diabetic regulation was begun by parenteral fluids and regular insulin as indicated, with subsequent disappearance of acetonuria and hyperglycemia during the first four hours of therapy.

Five hours after entry, the patient again vomited 750 cc. of bright red blood without clots. At this time, the pneumatic tamponade was inserted following the technique outlined above. Hourly gastric aspirations were done through the tube and after the first four hours, during which 5-10 cc. of dark blood was recovered each hour, bleeding apparently stopped. The position of the balloon was checked by fluoroscopy at this time and was found to be in the esophagus and well inflated. With the tube in place, it was possible to give small feedings of glucose directly into the stomach which in turn aided diabetic regulation. Eleven hours after insertion of the tube, 10 cc. of "coffee ground" material was again aspirated from the stomach. During the course of the next 5 hours, a total of 75 cc. more of this material was aspirated. An x-ray taken at that time revealed the balloon to be collapsed and resting in the stomach. When the tube was raised slightly and reinflated, it was ejected orally without gagging and vomiting. There were no adherent blood clots.

There were no further signs of active bleeding from this time on. He received 2,000 cc. of blood during the next two days with restoration of hematocrit and blood count to normal values. The stools became guaiac negative after the third hospital day and the remainder of his course was uneventful.

Mrs. E. W., age 73, was admitted to the DePaul Hospital in St. Louis, January 22, 1948, because of a fractured hip sustained in falling from a chair. Upon admission, the patient was questioned, but gave no history of abdominal pain, nausea, vomiting, distention, jaundice, or other abnormality. She had had an ulceration of the right ankle and right buttock which had been present for more than one year. Physical examination revealed an elderly white female who was moderately obese. The head, neck, heart and lungs were within normal limits. Abdominal examination revealed no masses or tenderness; the liver and spleen were not felt. There was mild distention of the abdomen but no signs of fluid were demonstrable. There was shortening and eversion of the right leg with trochanteric tenderness. There was a chronic superficial ulcer about 4 cms. in diameter on the right buttock and another similar lesion on the right pre-tibial area. On the day following admission an open reduction of the hip fracture with a Smith-Peterson nail was done. The postoperative course was uneventful until January 28th, when the patient vomited 100 cc. of altered blood. Further questioning revealed no history of chronic pulmonary disease or digestive disturbance. At the time of this first hematemesis, the blood pressure remained stabilized at 130/70 mm. Hg, and pulse 84 per minute. The liver and spleen were not palpable. The patient was placed on an acute ulcer

regimen. The following day she again vomited 500 cc. of dark clotted and bright red blood.

The next day there was another emesis of 1,200 cc. of blood. The patient was given repeated transfusions, in spite of which the blood count fell to 2,000,000 erythrocytes with 41% Hb. (Sahli).

Five days later, the patient again vomited 500 cc. of altered blood. Her condition remained precarious and on February 7th, there was further hematemesis. On this day, a pneumatic tamponade was placed in the esophagus. Examination revealed a palpable liver and spleen, mild icterus, evidence of a fluid wave in the abdomen, with edema of the ankles and sacrum.

Following the introduction of the tamponade, there was no further bleeding. Four hours later, gastric washings were clear and the patient was first given fluids through the tamponade tube which was kept in position for eighteen hours. It was then cautiously deflated and withdrawn. Her subsequent course in the hospital was uneventful.

SUMMARY

Massive hemorrhage from esophageal varices can be stopped by the use of a pneumatic tamponade. Coagulation is hastened by the local application of a thrombin preparation. Two cases are presented in which bleeding was successfully controlled by this method.

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ADDENDUM

Since preparation of this manuscript, the tamponade has been used successfully in four additional cases. Details of these will follow in a subsequent report.

Editorials

PRESENTATION OF FRIEDENWALD MEDAL TO DR. P. B. BABKIN

By

WALTER C. ALVAREZ

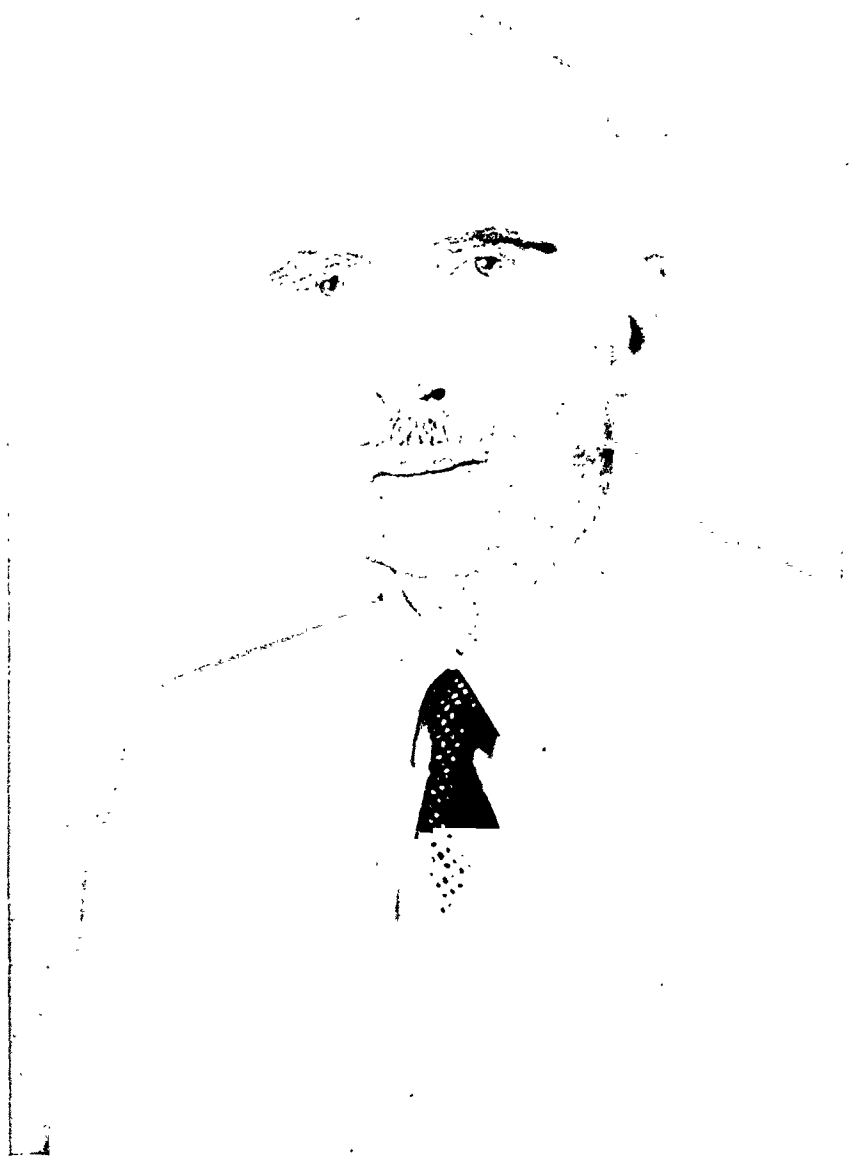
It is not an easy thing to get up before a group like this and, with a friend sitting near by, listening, to tell how much you like him and how much you appreciate his work. And yet we in America ought more often to attempt this. We ought to learn to break through our crust of reserve, and we ought to learn to say the kind words of appreciation that are in our hearts. I wish I knew how to do it better. I can only hope tonight that my great admiration for our guest and my years of friendship with him will shine through what I say, however ineptly I may say it.

My acquaintance with Dr. Babkin started many years ago when I began to read his fine articles on the digestive glands. I remember my joy on finding his splendid review article in Bethe's huge *Handbuch*. Later, in 1928, I received from Germany Dr. Babkin's masterpiece, the second edition of *Die äussere Sekretion der Verdauungs-drüsen*. It soon became one of my most prized and useful works of reference, with its 886 pages of well-documented information. I devoured it from cover to cover, and many times since I have gone back to it for help with a problem. Incidentally, I found it written in the most lucid German I ever read. Surely anyone who could make German lucid is "good." For that fact alone, our guest deserves several medals!

I then looked up what I could learn about Dr. Babkin, and found that he had been for years Pavlov's ablest and most eminent pupil and associate. He was the man whom Pavlov would like to have had as his successor. Because by nature I have always been a hero-worshipper and one who loves to know the men whose writings delight him, I soon made a pilgrimage to McGill University where our guest was then professor of physiology. There I found the quiet, modest, kindly, likable and clear-visioned man who sits here beside me tonight. We had what were for me delightful chats, and then he invited me to his hospitable home where I met his lovely and distinguished-looking wife and his sweet daughter. There I found a salon of interesting and intellectually inclined persons.

From his graduate students I learned of a devotion to their chief which was unusually fine. It was a devotion that does not wane with the years.

The students told me of happy evenings in the professor's home—evenings that, as you can imagine, meant so much to them. They told of the good, thoughtful conversation and of good food and drink. They told me of their



P. B. BABKIN

chief's beautiful playing of the balalaika and of his singing of Russian folk songs.

They told me that, like all really big men, he was decidedly able in several fields. He had such skill as a composer of music that, for a time, he thought of following this art as a career. The students told, also, of their teacher's great

knowledge of the Russian ballet (as a youth he was a ballet dancer), of his years of study of the physiology of musical appreciation, and of his great interest in the history of medicine.

I heard of a delightful sense of humor, of a great humility as a scientist, and of an honesty that caused him to keep saying often, "I do not know." I heard of his generosity in helping students to do their *Arbeiten*, and of his perfect fairness in assigning credit on the title pages of publications. As you all know, this is a sign of greatness. Later I was happy to get Dr. Babkin to come to our meetings here and to join in our discussions. A few years ago he published, this time in English, another fine work on the digestive secretions, now going into its second edition.

Today, past seventy, but still young in body and mental outlook, Dr. Babkin is working away in Penfield's Neurologic Institute at McGill. Still a student, he is an example to all of us older men of how well a man can use the years after his official retirement. Not content with all this, in spare time he has written a delightful volume on the life of Pavlov, a book soon to be published.

And now, Dr. Babkin, to you who have done more than any living man to throw light on the secretory mechanisms of the digestive tract, I take pleasure in presenting—on behalf of the American Gastroenterological Association—this Friedenwald Medal for distinguished service to science. With it goes the homage, respect and friendship of this group of men and women and of gastroenterologists and physiologists the world over.

GASTRIC AND DUODENAL ULCER: SIMILARITIES AND DIFFERENCES

For many years a lively disagreement has existed as to whether gastric and duodenal ulcer are the same. Certain anatomic differences have been emphasized, together with statistical variations in sex and age incidence, all of which seem of little practical significance. There are, however, a number of well established facts of considerable clinical importance.

Symptomatically, both lesions are characterized by epigastric pain. Rivers¹ emphasized a *tendency* toward different radiation, depending upon the location of the ulcer; this tendency may be looked upon as helpful, but not too consistent or reliable. Chronicity and periodicity are fairly constant features of the pain in both lesions and are related to the spontaneous healing and recurrence. The relationship between the intake of food and the occurrence of pain was formerly thought to be different in that in gastric ulcer the pain was alleged to come immediately after eating in contrast to the relief obtained from food by patients with duodenal ulcer. However, Sippy's² insistence that the so called food-relief-pain rhythm is identical in the two conditions

is now generally accepted. The pain mechanism, consisting of acid stimulation of exposed nerve endings, is the same in the two lesions^{3, 4}.

Etiologically, the essential role of acid gastric juice in the production of all chronic gastric and duodenal ulcers is well established. They do not occur in the persistent absence of acid gastric juice. Furthermore, complete anacidity, developing spontaneously, after radiation therapy or as the result of various surgical procedures, is followed by healing of the ulcer and by no recurrence for the duration of the anacidity.⁵ Thus, the lesions are in truth "peptic ulcers" and, in this respect, one and the same disease.⁶

There is, however, a marked difference in the secretory rate in the two conditions; the twelve-hour nocturnal secretion in duodenal ulcer is continuous and in terms of milligrams of hydrochloric acid, averages three and one-half times that found in normal individuals; in patients with gastric ulcer the output of acid in the fasting state is intermittent and is less than that observed in normal individuals. Thus true hypersecretion is present in duodenal ulcer, but not in gastric ulcer⁷. The explanation for this difference is not apparent. It is of interest, also, that in so-called intractable duodenal ulcer the basal gastric secretory rate may be two or three times the average rate for patients with duodenal ulcer, and approximately ten times that for normal individuals⁸.

The difference in the secretory rate in the two lesions suggests further that while in duodenal ulcer the hypersecretion, per se, may be able to break down the resistance of the mucosa, the situation in gastric ulcer is different: hypersecretion is absent, and hence other factors, such as a decrease in the resistance of the mucosa, may be responsible for the failure to withstand the acid attack. Konjetzny⁹, who postulates an inflammatory basis (gastritis and duodenitis) for both lesions and who considers the role of peptic activity to be minimal or absent, has not demonstrated a significant difference in the gastric mucosa in the two conditions. Guiss¹⁰, on the other hand, in similar studies, has noted the absence of atrophic gastritis in patients with duodenal ulcer, whereas it is frequently present in gastric ulcer. This observation corresponds quite well with our gastroscopic observations.

Another consideration of great practical importance is the fact that while duodenal ulcer is rarely confused with cancer, gastric ulcer always presents a serious problem in differential diagnosis. The occurrence of carcinomatous degeneration in gastric ulcer is still controversial; in duodenal ulcer, the question does not even arise.

Therapeutically, both lesions, if uncomplicated, respond satisfactorily to the same type of medical management. The complications are similar except for cancer, which, as mentioned, is not a complication but a problem in diagnosis. There is a marked difference in the tendency to the formation

of recurrent stomal or jejunal ulcers after gastroenterostomy for, as is well known, this complication rarely develops after posterior gastroenterostomy for gastric ulcer, whereas it is not infrequent when the same procedure is carried out for duodenal ulcer. Similarly, jejunal ulcers almost never develop after subtotal gastrectomy for gastric ulcer, whereas after partial resection for duodenal ulcer the recurrence rate probably exceeds 10 per cent unless one performs the extensive resection (75 to 80 per cent of the stomach by weight) advocated by Wangensteen¹². After complete vagotomy, as indicated by negative insulin tests, duodenal ulcers heal quite regularly, whereas in gastric ulcer the procedure is less satisfactory. These variations in surgical results all seem related to the vastly higher secretory rates in duodenal ulcer.

In conclusion, then, it seems clear that gastric and duodenal ulcer are the same disease in that they are both "peptic" ulcers. There is in the two lesions an unexplained fundamental difference in the fasting secretory rate of great practical therapeutic significance. Control of gastric secretion remains the key to the problem of peptic ulcer.

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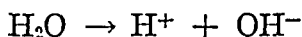
RECENT STUDIES ON THE MECHANISM OF HYDROCHLORIC ACID FORMATION BY THE GASTRIC GLANDS

For the past several years Davies and Crane and their coworkers in Professor Krebs' laboratory at the University of Sheffield in England have been studying the process of hydrochloric acid formation as it occurs in isolated pieces of gastric mucosa taken from frogs. This method of mounting an excised piece of mucosa in a glass chamber so that nutrient solutions can be placed on one side and secretions collected into a solution on the other

side, was first used by Delrue in France. The English workers have now perfected the technique so that measurements of ionic exchanges, oxygen consumption and carbon dioxide production, as well as electrical events can be accurately followed.

Many interesting observations have been reported by this group of workers. They found¹ that when the frog's gastric mucosa secreted acid *in vitro* aerobically it also produced an equivalent amount of alkali which was neutralized by CO₂ and passed into the nutrient solution as HCO₃⁻ ions. They also discovered that the ratio of the rate of oxygen uptake to the rate of hydrochloric acid formation was such that they concluded that it rendered untenable any theory (such as those proposed by Bull and Gray² or Conway³) in which the H⁺ ions are produced by oxidative degradation of fat, carbohydrate or protein. Not enough oxygen was consumed per unit of hydrochloric acid formed to provide all the H⁺ ions by such a means.

Davies' view¹ is that the reaction fundamentally concerned in the production of HCl in gastric mucosa is



The H⁺ are secreted and the OH⁻ ions are neutralized by CO₂ and passed into the nutrient medium as HCO₃⁻. This neutralization of OH⁻ by CO₂ is catalyzed by carbonic anhydrase. Thus Davies has been able to assign a specific function to this enzyme which, as has been known for some time, is present in the parietal cells in high concentration.

Interestingly, it was shown⁴ that at high rates of acid secretion not enough CO₂ was formed by cellular metabolism to neutralize all of the OH⁻ ions formed, so that some CO₂ had to be supplied from an external source. If, under these circumstances CO₂ was not supplied from an external source, the mucosa became damaged and in some cases even perforated, presumably due to the damage done by the accumulation of unneutralized OH⁻ ions.

It has been known for over a hundred years that a rather large electrical potential difference exists across the stomach wall, the secretory surface being negative. Rehm⁵ at the University of Louisville has studied this potential and its relation to acid secretion. He found that during acid secretion the potential difference falls and the resistance of the mucosa increases. He also showed that when he introduced a current from an outside source and passed it through the gastric mucosa, secretion of acid was enhanced when the current was in the same direction as the natural potential difference and inhibited when in the opposing direction. All of these findings were confirmed by the English workers^{6, 7} and they have proposed on this basis that this electrical energy, derived from the metabolic activity of the cell, is used in an electrochemical process which results in a net separation of H⁺ and OH⁻

ions at or near the canalicular membrane of the parietal cell. Some theoretical ways in which the cellular enzyme systems could accomplish this have been suggested^{7, 8}.

These recent studies mark a distinct advance in our understanding of the mechanism of hydrochloric acid formation by the gastric glands.

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DUODENAL ULCER: IS THE HYPER-SECRETION PSYCHOSOMATIC?

As yet no explanation is available for the fact that the majority of patients with duodenal ulcer have a higher basal secretion than normal¹. Dragstedt² concluded that it is chiefly of vagal origin because it is reduced profoundly by complete bilateral vagotomy.

There are several possible mechanisms whereby a vagal hypertonicity might arise. An elevation of the intrinsic basal activity of the vagal secretory nuclei would produce a continuous increase of nerve impulses and presumably a hypersecretion; but there is no experimental evidence at present to support this hypothesis. Another possibility is that of direct stimulation of the vagal centers by a change in the composition of the blood; the stimulating effects of hypoglycemia and of increased concentrations of amino acids are well known^{3, 4}; but here again, there is no evidence that either is responsible for the hypersecretion. Stimulation by secretagogues is a possibility; but these act directly on the parietal cells, not through the vagus.

Another possible explanation is that of reflex stimulation of the vagal centers. The classical experiments of Pavlov, confirmed many times, indicate that the vagal nuclei can be stimulated reflexly by the sight, smell, or taste of food; furthermore, certain stimulating conditioned reflexes can be established. Objective evidence has been presented by numerous investigators that emotional stress such as resentment, hostility, anxiety, fear and depressive thoughts can alter gastric function⁵⁻¹⁰ presumably by vagal excitation. The suggestion of various states to hypnotized individuals can elicit a gastric response. Heyer^{11, 12} produced an increased secretion with sham feeding of bouillon, bread and milk. The suggestion of pain and danger under hypnosis de-

creased secretion as did the suggestion of agreeable events. Luckhardt and Johnson¹³ produced increased secretion in response to the suggestion of a test meal. Bennett and Venables¹⁴ decreased secretion by suggesting a dangerous situation to a hypnotized army officer. Gordon and Chernya¹⁵ report a decrease in volume of secretion and anacidity following the suggestion of a state of complete rest and freedom of emotional conflict in three hypnotized patients. Wolf and Wolff⁹ showed that a prolonged state of emotional tension (namely, anxiety) in their subject Tom produced a simultaneous prolonged period of hypersecretion of acid; when Tom's anxiety was relieved, the secretion returned to normal.

These studies all suggest, therefore, that varying emotional states may either increase or decrease gastric secretion in a reflex manner, the type of response depending in part upon the nature of the emotional situation¹⁶ and in part upon many other factors such as the "tonus" of the vagal center and the condition of the peripheral secretory end organ, i.e. the glands themselves. Little is known, however, in quantitative terms, of the roles played by these various phenomena in the hypersecretion of patients with duodenal ulcer. One of the purposes of this editorial is to point out that in spite of the observations mentioned, there is as yet no proof that the excessive secretion is emotional in origin or that it is related to a "conflict situation", nor is there evidence that it can be reduced permanently or even transiently by psychotherapy of any type. Such studies are sorely needed.

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REGURGITATION AND RUMINATION

The gastroenterologist commonly sees women and a few men who say that they are vomiting. A little questioning, however, soon shows that they are not really vomiting but are regurgitating; that is, without any effort and usually without any nausea they are bringing up mouthfuls of food. They may continue to do this for two or three hours after a meal. Commonly, they begin to regurgitate while still at the table. Usually the person says that the regurgitation brings relief from epigastric distress. Some patients will admit that they could hold the food down if they had to, but others say it comes up in spite of every effort to hold it down. Others say they can hold it down, but then the distress in the stomach becomes too troublesome. Some of these persons stay plump or maintain their normal weight, while others lose weight and a few go down to skin and bones, especially if the condition becomes complicated with anorexia.

It is helpful to remember that this condition is functional in nature in practically 100 per cent of the patients. Very rarely one will see such a patient who has pyloric stenosis due to an ulcer, or has gallstones. An operation will relieve the gastric stasis or the colics, but usually the regurgitation will go on as before. It is very helpful then, in a given case, to recognize this type of so-called vomiting because it tells much about the diagnosis. It is like getting a history of globus hystericus which tells the physician that he is dealing with the type of person who is likely to have functional and hysterical troubles.

Oftentimes, the physician can draw from a regurgitator the story of hysteric attacks, and perhaps of a bad situation at home, which can help to account for the illness. In other cases the patient may appear sensible and may deny the presence of strain, and then it may be found that she regurgitates only when she is very tired or when she is menstruating, and there is a tendency to back pressure and reverse peristalsis in the digestive tract. Thus, a certain nurse learned years ago that whenever she starts regurgitating it means that she has been too long on a hard case; she must then stop and get a rest. When she is rested, the regurgitation disappears. There are other cases in which no good explanation can be obtained for the regurgitation. The patient may look strong and robust; she may ordinarily have a good digestion, and there may be no sign of a neurosis. In such cases one can sometimes get the history of a hereditary tendency toward the trouble.

In some cases, also, it has been found that some of the regurgitators in the family were ruminators; in other words, when the food came up it tasted so good that the person chewed and swallowed it again. One such woman said a strawberry tasted just as good the second time as the first time, and so she rather enjoyed her ability to ruminate. Although she had a perfect digestion,

when menstruating or badly constipated she might bring up and identify a piece of food that had been eaten thirty hours before. During some of her pregnancies she suffered much from the regurgitation of strongly acid gastric juice which burned her pharynx. Later in life she suddenly noticed that the juice was not acid any more and a test then showed that she had a marked achlorhydria. She still regurgitated. This woman's mother ruminated occasionally; one of her daughters (the third generation) vomited easily under excitement; her daughter (fourth generation) regurgitated badly every day for several years after she was born. We appear to have, then, a family in which for four generations there was a tendency toward regurgitation or rumination or vomiting.

In 1895 Runge¹ wrote of a scientist friend of his who ruminated. This man's father regurgitated his food, but refused to chew it and swallow it again. The scientist's son already was ruminating at the age of seven. Grand in 1889, in a Paris thesis, reported the case of a father and aunt and four children who were ruminators. In 1902 L. R. Müller^{2, 3} reported the case of a man and his two sons who ruminated. After his paper was published, Müller received a number of letters from persons who said they were ruminators. One man wrote that he, his mother and his sister ruminated. Another person, a man of 60 years, said he and his father ruminated. Apparently, rumination is not uncommon; it can be present for a lifetime and it is compatible with a perfect digestion. The person may have no objection to the habit, but his or her spouse may be annoyed or disgusted.

One wonders if this tendency toward regurgitation is a throwback to some of our animal ancestors who are in the habit of regurgitating their food, either to chew it again or to feed their young. Some animals of the camel family, when angered, have a special use for regurgitated food; when angered at someone they bring up a lot of foul material from the stomach and from a distance spit it all over the unfortunate offender.

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NERVOUS STORMS DUE TO PHEOCHROMOCYTOMAS

Of late, interest has been increasing in the pheochromocytomas of the suprarenal glands. The clinical picture is usually that of periodic episodes of hypertension, palpitation, marked anxiety and jitteriness, headache, vomiting, glycosuria and vasomotor storms. As one might expect, the picture is similar to

that produced by an injection of a dose of epinephrine. The disease is encountered usually in patients between the ages of 20 and 40 years.

An excellent paper on the subject is that by Howard and Barker. (Howard, J. E. and Barker, W. H.: Paroxysmal Hypertension and Other Clinical Manifestations Associated with Benign Chromaffin Cell Tumors [phaeochromocytoma]. *Bull. Johns Hopkins Hosp.* 61: 371-410 [Dec.] 1937.)

Early in the course of the illness weeks or months may elapse between the attacks, but as the disease progresses, episodes may occur daily or even several times a day. Among the factors precipitating the paroxysms may be emotional upsets, physical effort, the eating of a large meal, prolonged fasting, palpation of the tumor mass, or the assumption of positions of the body in which the tumor is compressed.

In attacks there may be an increase in the respiratory rate, with some dyspnea and marked acceleration of the pulse rate. In one fifth of the cases there is a slowing of the pulse rate. There may be nausea and vomiting, especially if the attack comes shortly after a meal. There is usually severe headache, which is generally occipital, but frequently involves the whole head. In the spells many of the patients complain of precordial and epigastric pain and cramps in the extremities. Usually there is frequency of urination, but sometimes there is suppression of urine.

In attacks the most marked finding on physical examination is, of course, the sudden elevation of both the systolic and diastolic blood pressures. Usually the systolic pressure goes above 200 mm. of mercury, and it may go even to 300 mm. The diastolic pressure goes up proportionally. With this there is often a pronounced distention of the veins of the neck, and frequently an increase in the circumference of the neck. In perhaps half of the cases there are signs of pulmonary edema. During the paroxysm, in half of the cases, there is hyperglycemia and glycosuria. This is due to the effect of the discharged epinephrine. After the disease has persisted for some time there may be extensive changes in the arterioles in the retinas.

In about 50 per cent of the cases a mass can be palpated in the region of one kidney. In other cases the pheochromocytoma occurs in other parts of the body. In some cases hypertension may not be paroxysmal but permanent, and in such cases the nature of the disease is likely to be missed. It may be suspected if a transient glycosuria is found or if there is a decided increase in the basal metabolic rate. A mild increase can be seen with any hypertension. All patients with severe hypertension should have an intravenous urogram made.

In puzzling cases Roth and Kvale (1945) suggested the use of an intravenous injection of histamine to induce an attack. Two minutes after the intravenous injection of 0.05 mg. of the drug, the blood pressure may shoot up and a characteristic attack may ensue. In normal persons the increase in blood pressure

will not be more than 6 or 12 mm. of mercury, while in the patients with pheochromocytomas it may be from 110 to 130 mm.

These patients are in a dangerous condition, because even a minor operative procedure may precipitate shock and death. The successful removal of the tumor in these cases is usually followed by a delightfully favorable result.

W. C. A.

BECAUSE OF SOARING COSTS OF PRODUCTION MANY ARTICLES WILL HAVE TO BE SHORTENED

The editors regret to have to announce that because of soaring costs of production and printing we cannot go on as we have been doing, publishing more and more pages to a volume. We hope later to be able to expand the journal again, but for a while we will have to cut down on the length of many of the articles submitted. In some cases, if authors wish to pay for additional space, this can be arranged.

Fortunately, most papers are not injured by shortening; actually, they are improved, and the author is benefited by the fact that many more persons will read a contribution which is brief and to the point. Recently, as we sat in the hall in Atlantic City and heard man after man present an excellent paper in 10 minutes, we thought of medical conventions thirty years ago, when the reading of papers took from 30 minutes to an hour and a half. Actually, then, no more of what was essential was said in an hour than is said now in 10 minutes.

In most cases a writer is wise if he cuts off the long introduction he wrote. Most papers could profit much from being beheaded. The best introduction is one which briefly calls attention to the need for certain information to fill a gap in our knowledge. The writer will say that he has tried to fill this gap or he thinks he has filled it. Occasionally he should say that there is a controversy on in which two or more views are held. The paper tells of an effort made to see which one of these is the most probably correct. Only occasionally need the author mention much of the history of the subject, and then he should give only enough to show why there was need for doing the bit of research that he is now reporting.

The worst thing a man can do is to write a long introduction, made up of material which everyone knows, such as that the etiology of a disease is obscure. All this does is to cause men to lose interest, and to stop reading. They never get to the meat of the article. The wisest writer tries, with a pithy sentence or two, to grip the interest of the reader so that he will want to read the article.

The next thing is not to put in any extraneous or uninteresting material which will cause the reader to stop and move on to the next article in the journal. Many men do this by inserting a long discussion of the literature or a page or two of tiresome details about technic, which cannot interest anyone

except those few men who are doing research in this field and who may want to repeat the experiments. It would seem best, then, to describe laboratory technic in a note at the end of the article where it will not interrupt the flow of the argument.

Another thing that writers need to avoid is the inclusion of material foreign to the topic. For instance, a man writing on carcinoid tumors of the ileum may describe a case of terminal ileitis which he ran onto during his study. His article is no place for that. Occasionally a paper is sent in which should be cut up into four or five separate papers, each on a different subject. What many writers fail to think of is that anything published without an appropriate title which will be well listed in the cumulative index is buried and lost. Because it is lost it will have no influence on medical thought. For instance, Jacobi, who discovered the interesting reverse peristalsis in the right side of the colon, hid it away in an article on Colchicum poisoning! The wise writer, then, keeps extraneous material out of his article (1) because it is wasted there, and (2) because it can only distract attention from the matter in hand. Anything that distracts the reader is bad for the author.

Many a discussion of the literature with a large bibliography should be left out. It would be much better to say that a bibliography of 300 titles is to be found in a recent article by so and so.

Long tables should often be left out because few readers will stop to study them. Sometimes the data in several tables could, with great advantage, be shown in a graph or two. Tables are very expensive to print.

Discussions should often be shortened, with advantage to everyone. Efforts to explain things as due, let us say, to paralysis or stimulation of the autonomic nerves had best not be made. It is better to report findings and let future research show what they mean. Often the arrogant claims of a writer, or dogmatic statements and interpretations and theorizings only antagonize the able readers whom he wants most to impress favorably.

The summary should be written with the greatest care because today most readers and most abstracters look only at this part of the article. If, then, a writer fails in his summary to include mention of all the important things he found, he is cheating himself.

Most case reports could be greatly shortened with advantage to everyone. For instance, let us say a man saw a case in which a colonic diverticulum ruptured into the stomach. That would be interesting, and probably worth reporting, but this could probably be done on a page or two. All that is needed is to tell briefly what the symptoms were *which might be attributed to the lesion*. No one wants to hear about the man's varicose veins or his bunion. The doctor will describe briefly only the *essential findings* which led to the diagnosis—if it was made before operation or death. The findings at operation or necropsy

will again be described briefly and all extraneous matter will be left out. The readers will not care to know just when the patient was admitted to the hospital, what doctor sent him in, and what his family were like. It is very doubtful if anyone will want to know about the findings which had no significance. Many a reporting clinician appears to want to show his fellows how thoroughly he works up his cases, but the editor to whom he sends his report is anything but well impressed. In many case reports of purely medical interest the reader is told what anesthetic was used, how the abdomen was opened and closed, and how many liters of salt solution were given intravenously. Who wants to know about that? Similarly, in the report of the necropsy, no one wants to know all the details about the whole body. The readers are interested in two things: (1) how the diverticulum came to rupture into the stomach, and (2) how they might recognize a case of this disease if they ever see one.

The editors are very grateful to all those writers who in the past have cooperated in so friendly a manner in the shortening of papers. They crave indulgence for the future.

Comment

Readers are invited to contribute to the Comment Section of Gastroenterology short notes expressing their opinions on controversial topics and matters of current general interest.

IS THE HYPERSECRETION OBSERVED IN DUODENAL ULCER PATIENTS DUE TO EXCESSIVE VAGAL STIMULI TO THE STOMACH?

It is now well agreed that the abnormally high volume and concentration of hydrochloric acid secreted by many duodenal ulcer patients can be reduced to or below normal by complete transection of the vagus nerves¹. This has been considered by some to constitute crucial and final proof that the elevated secretory rate in these patients was due to excessive activity of the vagal secretory nerves to the stomach. Is this conclusion valid?

There are two reasons why this concept cannot be considered to be proven. First, the increased secretory activity of the stomach in duodenal ulcer patients is not confined to those types of stimuli which depend upon the vagi for their mediation. For example, the response to histamine is as greatly elevated as is the response to insulin². Similarly the basal secretory activity, the nocturnal secretion, the response to caffeine, the response to test meals of food or alcohol; all are, on the average, elevated above normal. It may be said that the secretory cells of the stomach of the duodenal ulcer patient manifest a hyper-reactivity to any and all stimuli.

Second, and conversely, vagotomy does not merely reduce the secretion due to vagal stimuli. It *abolishes* the responses which depend upon vagal pathways, such as the response to insulin or sham feeding, but it also *greatly reduces* the response to all other stimuli including histamine, caffeine, and food³. Because of this fact, we should expect vagotomy to greatly reduce the secretory responses of the duodenal ulcer patient regardless of whether the excessive secretion was caused by too many vagal nerve impulses or by some stimulant which circulated in the blood and acted directly upon the secretory cells.

The question of the cause of hypersecretion in duodenal ulcer cannot be considered to be settled.

M. I. GROSSMAN, PH.D., M.D.

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Book Reviews

BIOCHEMICAL EVOLUTION: *Marcel Florkin*. Edited, translated and augmented by Sergius Morgulis. Academic Press, Inc., New York. 1949. pp. 157. Price \$4.

This is a fascinating, most valuable and most unusual book. It is remarkable how few men have been interested in the evolution of biological chemistry as it can be observed in plants and animals. About the only one in this country who much concerned himself with the problem was Gideon Wells of Chicago.

Florkin and his students and Morgulis have done a great deal of work on the subject, and altogether they have used material from 291 articles.

It is interesting to see that in many ways the most primitive of plants and even bacteria solve their metabolic problems much as we humans do. As animals became ever more complicated they had to develop kidneys to get rid of waste products. Some of them got rid of these products in the form of ammonia; others in the form of urea, and others in the form of uric acid. The larger animals had to transport oxygen from the gills or lungs to the tissues and in order to do this some of the simpler sea dwelling animals used hemocyanin which contains copper. The higher animals developed hemoglobin which contains iron. Interestingly, the chlorophyll which in plants serves to build CO_2 into carbohydrates somewhat resembles hemoglobin in its chemical structure.

There is evidence to show that as plants and animals evolved and became more complicated, some of their body chemistry also evolved and became more complicated. Actually, a study of biological chemistry in the various species helps in the classification of plants and animals. Light is thrown on the relations of certain genera, one to another, and on the road that some followed during millions of years of evolution.

Every philosophically minded physician or biologic chemist will certainly want to study this book.

ERNAHRUNGSLEHRE UND DIATETIK. *Dr. M. J. Demole, Prof. Dr. A. Fleisch and Dr. Cl. Petitpierre*. Medizinischer Verlag Hans Huber, Bern, 1948. pp. 382.

This is a typical German book on diet, which contains a lot of information. About the only feature that will bother some American readers will be the over-specialization of diets. For instance, one finds diets for acute diarrhea, chronic diarrhea, fatty diarrhea and sprue. Then one finds diets for atonic constipation, spastic constipation, constipation with colitis and chronic colitis. One finds diets for hepatitis, hepatismus, cirrhosis of the liver and diseases of the gallbladder. One finds diets for hyperacidity and hypersecretion in the stomach, also for anacidity and for gastrectasis. The more thoughtful type of gastro-enterologist will look upon this remarkable specialization of diets as a sign of lack of cerebration.

AUREOMYCIN—A NEW ANTIBIOTIC. *B. M. Duggar, et al.* Annals of the New York Academy of Sciences. vol. 51, Art. 2, pp. 175-342.

This is a splendid monograph on one of the new antibiotics. It will be of tremendous interest to anyone who is taking care of patients with acute infections.

THE CHEMOTHERAPY OF FILARIASIS. *L. L. Ashburn, et al.* Annals of the New York Academy of Sciences. vol. 50, Art. 2, pp. 19-170.

This book of course, will be of interest almost entirely to men working in the field of tropical disease.

HOW TO CONQUER YOUR HANDICAPS. *Marie Beynon Ray.* The Bobbs-Merrill Company. Indianapolis and New York. 1948. pp. 336. Price \$3.00.

This is a book by the woman who wrote *How Never to be Tired* and *Doctors of the Mind*. Her theses are that no one succeeds without some handicap and your handicap is your opportunity. She writes with skill and interest and great enthusiasm, but she probably forgets that only one man in a million, endowed with tremendous will power, is likely ever to become a great orator when he was born to be a stammerer.

However, it may help some persons to know what has been done by some handicapped men and women, and it may bring hope to many.

One splendid thing that Marie Beynon Ray has done has been to consult with a large number of doctors and others who could give her first hand information. Excellent is her chapter on the problems of the stutterers.

At times the reader will become doubtful about some of the stories, but on page 308, Marie Beynon Ray says, "Don't take my word for any of these stories,—I don't believe them myself. But there they are, spread out on the record for all to read."

Very valuable is the list given at the end of the book, of places to which one can write if one wants more information; for instance, in regard to speech disorders, or a company that will employ a handicapped man or woman.

Certainly everyone who is interested in rehabilitation should read this book.

INTERESTING AND USEFUL MEDICAL STATISTICS. Edited by *William H. Kupper, M.D.* William C. Brown Company, Dubuque, Iowa. 1948. pp. 528. Price \$6.50.

This is a curious and unique book. Apparently, Dr. Kupper, for years, has been much interested in medical statistics, and whenever he saw a table somewhere that interested him he put it into a scrapbook. This is the scrapbook with a short preface.

Obviously, this is a book not for reading but for the reference library.

COMPARATIVE PSYCHOLOGY OF MENTAL DEVELOPMENT. *Heinz Werner, Ph.D.* Revised Edition. Follett Publishing Company. New York, Chicago, Los Angeles. 1948. pp. 564.

This book by the Professor of Psychology at Clark University is an unusual study

carried out along unusual lines. The author compares the thinking of children, of primitive men, and of certain psychotics. In all three groups he finds certain types of thinking which he labels with long Latin names. The important point is that the type of thinking common to all three groups is not satisfactory for a civilized adult because it does not help him to discriminate what is essential from what is non-essential. Most of what is wrong with civilization today is that the great bulk of persons are unable to think as adults and behave as adults. There are too many who cannot learn enough, and there are too many who think, as children do, that in some magical way they or someone else can get for them whatever they want.

The one unfortunate thing about this very learned book is that the author knows so many long words and loves to use them. This could be so immensely better a book if someone could rewrite it in simple English. It probably would then be very interesting. Would it not be a joke on the writer if one of the signs of adult thinking is to use simple everyday words!

ABSTRACTS OF CURRENT LITERATURE

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MOUTH AND ESOPHAGUS

BEELER, R. C., COLLINS, J. N., AND HALL, M. F. Benign pedunculated tumors of the esophagus. *Am. J. Roent. Rad. Therapy*, 60: 466 (Oct.) 1948.

Pedunculated tumor of the esophagus is rare and may be encountered unexpectedly on routine examination, since, in most cases, symptoms are mild or not elicited. Tumors of this type arise in the uppermost portion of the esophagus due to redundancy and elasticity of the esophageal mucous membrane in this region which is greater there than in any other part. Grossly, these tumors are smooth, about one inch in diameter, variable in length, and may have multiple projections distally. Microscopically, most pedunculated tumors arising from the hypopharynx are fibrolipomas. A correct diagnosis is important because the tumors are amenable to surgical treatment in most cases.

FRANZ J. LUST

STOMACH

GRAY, H. K., MEYERS, W. C. AND DOCKERTY, M. B. Postgastrectomy gastritis. *Surg. Clinics N. Am.*, 965 (Aug.) 1948. The authors present a study of 25 patients, taken at random, who had undergone gas-

tric resection and returned later because of persistent gastrointestinal symptoms. Most of the resections had been performed for duodenal ulcer, and microscopic examination revealed gastritis in all 25 cases. It is therefore recommended that all gastric resection specimens be examined histologically and that rigid postoperative management be maintained where gastritis is found.

Roentgenologic examination was found to be of little value in determining the presence or absence of gastritis following a partial gastrectomy. In the cases reported, gastroscopic examination revealed a normal stomach in one case, an indeterminate lesion in another case and, in the remaining 23 cases, a postoperative gastritis or gastrojejunitis was found which was of sufficient severity to account for the patient's distressing symptoms.

Treatment is slow but the problem is not hopeless. Reassurance and rest plus the proper diet and medication can accomplish a great deal.

FRANK G. VAL DEZ

HOWES, E. L. AND DE OLIVEIRA, J. R. Early changes in the experimentally produced adenomas and adenocarcinomas of the stomach. *Cancer Research*, 8: 419 (Sept.) 1948.

Silk threads containing methylcholanthrene produced new growths when embedded in the wall of the rat's stomach. The adjacent early changes were studied in an attempt to disclose the mechanism of formation of new growths in the stomach. Shortly after implantation beneath the serosa, round cells infiltrated and edema appeared. Ulceration occurred in the mucosa and then the superficial mucous cells on either side grew into the defect to form an epithelial-lined cleft. Acid and pepsin cells were destroyed and did not grow downward. If a thread perforated the mucosa or the ulceration occurred directly over a thread that remained in position, the superficial mucous cells grew back along the thread to form an epithelial-lined sinus. In the clefts, these cells formed a new mucosa composed entirely of mucous cells, while the sinus was filled with a cylinder of these cells arranged in acini. This process took approximately 2 weeks and the cells showed no malignant changes. After 35 days, adenomas formed in the clefts and adenocarcinomas formed in the sinuses. Adenomas grew outward toward the lumen of the stomach, pushed open the mouth of the cleft, and sometimes filled the lumen of the stomach. This type of growth did not disturb the reticulin boundary that had been formed beyond the new mucosa lining the cleft. Adenocarcinomas grew within the wall of the stomach and the reticulin barriers, already formed about the sinus, were destroyed.

JOSEPH B. KIRSNER

GRAY, H. K. AND LOFGREN, K. A. The significance of an ulcerating lesion in the stomach after gastroenterostomy. *Proc. Staff Meetings Mayo Clinic*, 23: 454 (Oct.) 1948.

The coexistence of an active duodenal ulcer and a gastric carcinoma is quite rare. Patients with duodenal ulcer are much less likely to develop cancer of the stomach than those who have no stomach disease whatever. Statistics at the Mayo Clinic reveal that duodenal ulcer and gastric ulcer are associated together twelve times more commonly than are duodenal ulcer and gastric carcinoma. During the 10-year period, 1938

-1947, a total of 825 patients were seen who had had a gastroenterostomy previously performed for peptic ulcer and in whom a subtotal resection was now performed. The complications for which secondary resection was performed were present in the following descending order: jejunal ulcer, malfunctioning gastroenteric stoma, gastric ulcer, and gastric carcinoma. Forty-one gastric lesions developed after gastroenterostomy for duodenal ulcer, of which 11 (27%) were gastric carcinomas and 30 (73%) were benign gastric ulcers. In 11 patients, gastric lesions developed after gastroenterostomy for gastric ulcer. In 5 of these patients, the new lesion was found to be another benign gastric ulcer, whereas in the remaining 6 cases, a malignancy had developed. These statistics reveal that a high incidence of gastric malignancy is found among recurrent lesions following gastroenterostomy for peptic ulcer. Therefore, every lesion in the stomach after gastroenterostomy should be suspected and treated as a malignant one until proven otherwise.

FRANK NEUWELT

CANNEY, R. L. Neurogenic tumors of the stomach. *Brit. J. Surg.*, 36: 139 (Oct.) 1948.

Benign tumors of neurogenic origin are rare. Two types are described, neurilemmoma and neurofibroma associated with von Recklinghausen's disease. They probably arise from the sheath of sympathetic nerve fibres. Grossly they are polypoid, may be multiple, occur any place in the stomach, and are often indistinguishable from leiomyomata. There are no characteristic clinical features and final diagnosis usually requires histological study. Resection is the treatment of choice; locally, if the tumor is small and widely, if malignant change is suspected. Two patients with gastric neurogenic tumor are described. In one patient with a history of hematemesis and melena, a neurilemmoma undergoing malignant change was found; in the other with an unexplained anemia, the gastric tumor was considered a local manifestation of von Recklinghausen's neurofibromatosis. In the latter patient, typical nodules of von Recklinghausen's dis-

ease developed on the trunk, abdomen and back 11 years later.

C. WILMER WIRTS, Jr.

SINGMASTER, L. A suction and feeding tube for the postoperative care of gastric resections. *Surgery*, 24: 621 (Oct.) 1948.

The immediate management of patients who have had gastric resections is concerned with adequate intragastric drainage and supplying the nutritional requirements of the patient until sufficient oral feeding is possible. Utilizing a size 18 French double-lumen tube, 52 inches in length, both of these problems were adequately solved. The distal end of the tube terminates in a hard rubber tip, sealing a 3-inch column of mercury within the tube. Just proximal to the mercury column are perforations for feeding, and 13 inches from the tip is another series of perforations for intragastric suction. The feeding lumen terminates at the perforations at the end of the tube, while the suction lumen, of larger diameter, terminates at the higher perforations.

Preoperatively, following preparation with the Levin tube, the double-lumen tube is passed to just within the stomach where it lies *in situ* during the operation. Before closing, the tube is advanced into the jejunum until the suction perforations lie just proximal to the line of anastomosis. The suction lumen is handled as an ordinary stomach suction tube. The feeding lumen is opened 10 hours postoperatively when high protein and high caloric liquid feedings are introduced. Parenteral fluids and orogastric liquid feedings are administered concomitantly. This tube can be used for gastroenterostomies as well as gastric resections.

A. I. FRIEDMAN

BOWEL

DIXON, C. F. AND MEYER, A. C. Volvulus of the cecum. *Surg. Clinics N. Am.*, 953 (Aug.) 1948.

Volvulus of the cecum is described as a rare and urgent problem of intestinal obstruction, which has a high mortality rate largely because it is infrequently considered and diagnosed. A long mesentery is necessary for its occurrence and anything which

distorts the already mobile cecum may be an exciting cause. The signs and symptoms are those of a low intestinal obstruction. Location of pain may vary but remains where it begins. The absence of vomiting and the passage of gas and feces does not preclude the diagnosis early in the disease. The enlarged cecum may present itself as a palpable mass. Dilated loops of bowel may be seen with X-ray, but establishment of a definite diagnosis by this means is rare.

The best treatment is simple detorsion and fixation, if this is possible and if there is no gangrene. In the presence of gangrene, resection over a three-bladed clamp is the safest procedure. Intermittent volvulus of the cecum does occur and a new operative procedure is suggested for its correction.

FRANK G. VAL DEZ

DIXON, C. F. AND JUDD, D. B. The surgical treatment of congenital megacolon.

Surg. Clinics N. Am., 889 (Aug.) 1948. Congenital megacolon is described as a dilatation and hypertrophy of part or all of the colon, and is thought to be due to an imbalance in the nervous mechanism supplying the colon. Medical measures in the treatment of this disease have been variable and generally discouraging.

Lumbar sympathectomy has been tried, but, in the series of 26 cases reported, only 1 patient had a satisfactory result. Fifty-four cases of resection are reported in which the diseased portion of the bowel was removed, and of these patients, 78 per cent were improved, including 67 per cent who were completely relieved of symptoms. The mortality rate of this series was 4 per cent. The operation should not be performed on patients under 3 years of age, because of high mortality in this group. Five years is believed to be the optimal age but surgery should not be prolonged in the presence of severe or persistent symptoms. In the 54 cases operated, there were 41 in which half or less of the colon was removed and there has been no evidence of recurrence of the disease in the remaining portion of the colon.

The authors, therefore, believe that resection of the diseased portion of bowel is the treatment of choice in congenital megacolon.

FRANK G. VAL DEZ

POSEY, E. L., JR. AND BARGEN, J. A. Jejunio-ileac insufficiency; its relation to the sprue syndrome. *Surg. Clinics N. Am.*, 903 (Aug.) 1948.

The various causes which may produce a deficiency state akin to the sprue syndrome are given. The symptoms of jejunio-ileac insufficiency are protean and include fatty diarrhea; microcytic anemia, which may be due to loss of iron; macrocytic anemia, due to loss or defective absorption of the erythrocyte-maturation factor or gastric achlorhydria; tetany; and various vitamin deficiencies. The amount of small intestine which can be removed without causing jejunio-ileac insufficiency varies greatly in different cases.

Strictures of the small intestine may produce severe deficiency states but symptoms of intestinal obstruction will not be present unless the stenosis is marked. Intestinal short-circuiting, such as gastro-jejuno-colic fistula, frequently produces deficiency states with symptoms resembling those of sprue. Diseases of the wall of the small intestine such as tuberculosis, regional enteritis and enterocolitis occasionally cause deficiency states. Malignant tumor of the small intestine rarely causes the syndrome. The development of the deficiency state is influenced by the dietary regimen employed postoperatively, as well as the amount of small intestine resected.

FRANK G. VAL DEZ

BINKLEY, G. E. Diagnosis and treatment of colon polyps. *N. Y. State J. Med.*, 48: 2145 (Oct.) 1948.

Polyps occur most frequently in the rectum and lower sigmoid, the most common type being adenomata. The symptoms are improper elimination and a change in the bowel rhythm; diarrhoea alternating with constipation may be present. Bleeding from the rectum at irregular intervals is another important symptom. Sigmoidoscopy and X-ray examination will reveal the vast majority of polyps. If accessible to the sigmoidoscope, polyps may be removed by the electric cautery snare; but those higher up require laparotomy. The pre-operative preparation of these patients must be as thorough as for operations for cancer

of the bowel. Colotomy with excision of the polyp is sufficient in the majority of single polyps. Right hemicolectomy may be necessary in cases of a single large or multiple small polyps located in the cecum, ascending colon, or proximal transverse colon. If these lie in the left half of the colon, resection and end-to-end anastomosis may be employed. Multiple polyposis requires total colectomy; sometimes the rectum may be retained in these cases.

PHILIP LEVITSKY

REID, D. R. K. Argentaftinoma of the gastro-intestinal tract. *Brit. J. Surg.*, 36: 130 (Oct.) 1948.

Of 25 cases of argentaftinoma of the gastro-intestinal tract, 8 were extra-appendicular in site, 6 involved the ileum, and 1 each the stomach and colon. The incidence, pathology and treatment are discussed.

Symptoms, due to the growth in the ileum, were present in 5 and absent in 1 case. Of these, 4 cases had primary acute intestinal obstruction, 4 had recurrent colicky abdominal pain, vomiting and flatulent dyspepsia for periods varying from 6 months to 8 years, 4 patients had a palpable abdominal mass, 3 significant weight loss, but only 1 case had bleeding from the bowel. In the 2 patients under 40 years, the lesion was benign and they were alive and well 2 years and 16 months after operation respectively. The other four patients had malignant growths and were over 50 years of age; one died after operation, one 9 years after the commencement of symptoms, and one is alive and well 8 years after operation. The remaining one could not be traced.

C. WILMER WIRTS, JR.

GROSS, R. E. AND WARE, P. F. Intussusception in childhood. Experiences from 610 cases. *New Eng. J. Med.*, 239: 645 (Oct.) 1948.

In contrast to intussusception in adult life, when in over one-half of the cases the cause is Meckel's diverticulum or various types of tumors, intussusceptions in childhood can rarely be accounted for by mechanical factors. The common theories involve enlarged Peyer's patches, ileocecal neuromuscular dysfunction, enteric infection, ex-

cessive catharsis and transition from breast to bottle feeding.

In the authors' series, 84 per cent of the cases occurred in the first two years of life, and 68 per cent between the third and eleventh months. Most of the patients were males. In intussusception the history is so characteristic that from it alone the diagnosis can be made. Characteristically, in over 95 per cent of cases there is sudden severe, paroxysmal abdominal pain in a previously healthy infant of superior nutrition and development. Vomiting is an early symptom and occurs in over 90 per cent of patients. With passage of time and increase in obstruction, pallor, sweating and restlessness are found as the child approaches a state of shock. In neglected cases of several days standing, a moribund state ensues with collapse and severe dehydration. Blood in the stool is present in about 85 per cent of cases, and in gross and copious in about one-half of the cases. The first stool after onset is usually normal, but the following stool will usually reveal blood. While often mild, the hemorrhage may be exsanguinating. An abdominal, non-tender mass is felt in about 85 per cent of the patients. When the intussusception is in the region of the splenic or hepatic flexures, the mass may be difficult to outline. In about 25 per cent of cases the mass can be found on rectal examination, and in 6 per cent of cases the mass protrudes from the anus.

The authors give a detailed description of the operative procedures. The optimum treatment of intussusception is by surgical reduction of the intussusception after rapid but important preoperative preparation. If resection is necessary, exteriorization is the method of choice, since this rigidly prevents contamination or soiling of the peritoneal cavity. Postoperative care includes the use of gastric suction, transfusion of blood or plasma, infusion of glucose or saline solution and in some cases institution of chemotherapy and placement of the child in a high-concentration oxygen tent.

The mortality rate for intussusception has improved steadily; in the last few years it has been reduced to 2.7 per cent.

ANTHONY M. KASICH

BLOOMFIELD, A. L. AND LEW, W. Cure of ulcerative cecitis of rats by streptomycin. *Proc. Soc. Exp. Biol. Med.*, 69: 11 (Oct.) 1948.

Ulcerative cecitis of rats is exquisitely chronic and interferes little with the general health of the animals. In 1940-41, cecitis became prevalent in the Stanford rat colony. Very young animals were not affected, but at 4-5 months of age, 44 per cent of the stock had fresh lesions and the incidence increased so that 66 per cent of 7-8 month-old rats showed lesions. Cultures from the ulcerations yielded *Salmonella enteritidis*. If *Salmonella* isolated from rats with cecitis is introduced into the drinking water of unaffected animals a violent diffuse enteritis, which in no way resembles the spontaneous disease, occurs. Rats, which survive, gradually develop the usual lesions but with no greater frequency than uninoculated controls. Organisms have not been obtained from fluid aspirated from cysts which often develop around the cecum. The development of cecitis was inhibited in rats on a vitamin B deficient diet. Cecitis could be prevented by incorporating succinyl sulfathiazole (1%) in the stock diet. Sulfaguanidine (0.5%) was equally effective. If sulfaguanidine was added to the diet of the mothers during pregnancy and lactation, the young subsequently failed to develop cecitis.

In the fall of 1947, cecitis was again present in the colony, the frequency in 4-5 month-old rats was now 83 per cent. Many animals showed very advanced lesions. These lesions resolved within 10 days of treatment with streptomycin added to the drinking water.

H. NECHELES

HUNT, C. J. Early diagnosis and roentgen manifestations of obstruction of small bowel. *Arch. Surg.*, 57: 460 (Oct.) 1948. The symptoms and physical signs of small bowel obstruction may be divided into three characteristic manifestations—pain, peristalsis and borborygmus. The pain is in no way related to any other type of abdominal pain, being generalized, diffuse, spasmodic and not associated with tenderness or muscle spasm. No other form of abdominal colic

has this characteristic of diffuseness, periodicity and relatively negative physical observation. Corresponding to the periodic spasm, there occur synchronously visible peristaltic waves and audible sounds of borborygmus. The roentgenogram is the only means by which one can make an early diagnosis of small bowel obstruction and can determine accurately the type of obstruction present. Gas can be demonstrated normally in the stomach and colon but not in the small intestine; there is nothing physiologically or anatomically wrong with the bowel distal to the obstruction, and it may function in an evacuating capacity with or without stimulation. Thus, the passage of gas or evacuation of the bowels, either spontaneously or by enema, may occur and give a false sense of security as bowel patency. In advanced simple obstruction, intestinal decompression is used prior to surgical treatment. In strangulated obstruction, immediate operation is imperative. The indications for the use of the Miller-Abbott tube are mentioned.

ALBERT CORNELL

OLSAN, E. S. AND SUSSMAN, M. L. Non-specific enterocolitis. *Am. J. Roent. Rad. Therapy*, 60: 471 (Oct.) 1948.

A case is presented of apparent chronic granulomatous jejuno-ileitis which, at post-mortem examination 5 years later, showed no evidence of this disease but revealed an enterocolitis of undetermined nature. The lesion in the large intestine was classified as ulcerative colitis. Chronic granulomatous disease of the small intestine until now has been considered to be characterized by stenosis. The present case indicates the possibility that resolution without stenosis can take place. The alternative explanation presumes it to be a disease, possibly a variety of ulcerative colitis, in which the small intestinal lesion dominates the roentgen findings, passing through a phase of thickening and rigidity to a normal or thin small intestinal wall.

Two cases of granulomatous jejuno-ileitis, and one of ulcerative colitis, with amyloidosis are presented. It is suggested that amyloidosis in chronic enteritis is more frequent than has been suspected and might

account, in part at least, for the clinical and roentgenographic findings in occasional cases of granulomatous disease.

Five cases are reported of extensive involvement of jejunum and ileum in ulcerative colitis. In one of these there was the possibility that the lesions were due to shock, and another was complicated by amyloidosis, but it seemed likely that the remaining cases represented extensions of the primary colonic disease.

The roentgen appearance of stenosis in the small intestine does not necessarily indicate granulomatous disease. Even in the absence of disease of the terminal ileum, ulcerative colitis cannot be excluded, despite the lack of distinct roentgen evidence to indicate its presence in the large intestine. Presumably the small intestinal deformity is due to edema and infiltration without significant fibrosis. These observations indicate that it is difficult to determine the type of enterocolitis from the roentgen appearance alone, and that even with postmortem data the pathogenesis may not be ascertainable.

FRANZ J. LUST

LIVER AND GALL BLADDER

COLCOCK, B. P. Choledochostomy: Its place in surgery of the biliary tract. *Surg. Clinics N. Am.*, 641 (June) 1948.

A technic for common duct exploration is described. The author believes that in the hands of a capable surgeon, exploration of the common duct does not appreciably increase the mortality or morbidity of gall bladder surgery. The indications for exploration of the common duct in biliary tract surgery are discussed. They include: (1) the history or presence of jaundice (either clinical or as a laboratory finding); (2) the finding of a dilated or thickened duct, possibly indicating a common duct stone; (3) other positive or suspicious findings on palpation of the common duct; (4) small stones in the gall bladder; (5) sediment in bile aspirated from the common duct; (6) acute or subacute pancreatitis; and (7) non-calculous gall bladder with biliary tract symptoms.

FRANK G. VAL DEZ

TWISS, J. R. AND CARTER, R. F. The diagnosis and management of the postcholecystectomy syndrome. *N. Y. State J. Med.*, 48: 2245 (Oct.) 1948.

The postcholecystectomy syndrome is defined as a symptom complex referable to the biliary tract which occurs after cholecystectomy. This report is based on 295 cases, of which 159 presented postcholecystectomy symptoms. The principal causes of symptoms postoperatively are: (1) dyskinesia of the sphincter of Oddi, (2) calculi in the bile passages, (3) retained cystic duct, (4) common duct stricture, (5) cholangitis, and (6) pancreatitis. The clinical findings and treatment of these six groups are discussed.

As a means of preventing postcholecystectomy syndrome, the presence of stones or infectious cholecystitis, with or without a concomitant cholangitis, should be promptly diagnosed and cholecystectomy performed before complications develop. The diagnosis of infectious biliary tract disease can only be confirmed by cultures of duodenal bile. On the other hand, functional disorders should be recognized as such and treated medically.

Symptoms of pain and colic, nausea, vomiting, and fat intolerance were more prevalent in the dyskinesia group; jaundice, chills, fever, pruritis, and biliary fistula are more characteristic of organic obstruction. There is also tenderness in the right upper quadrant, and an enlarged liver at times. Pathologic organisms are found in the bile drainage, and malignant cells have been recovered in cancer cases. Blood chemistry studies reveal elevation in serum bilirubin, alkaline phosphatase, and blood cholesterol.

Seventy patients were classified as belonging to the dyskinesia group. In 11 patients, the postoperative symptoms were due to common duct stones. Retained cystic duct was found in 8 cases. There were 9 cases of benign fibrous stenosis and 23 of common duct injury. Thirty-four cases of active cholangitis were found in association with biliary tract obstruction. The offending organism was *E. coli* in most cases; however, *E. typhosus*, *B. welchii*, *streptococcus*, and *staphylococcus* were also encountered. There were 15 cases of inactive

(asymptomatic) cholangitis. The most common organism here, too, was *E. coli*. Pancreatitis was responsible for symptoms in 3 individuals with organic obstruction to the common bile duct.

PHILIP LEVITSKY

HALLENDORF, L. C., DOCKERTY, M. B., AND WAUGH, J. M. Gangrenous cholecystitis: A clinical and pathologic study of 100 cases. *Surg. Clinics N. Am.*, 979 (Aug.) 1948.

In 100 cases studied, it was found that gangrenous cholecystitis had an incidence of 2.5 per cent of all cases operated for gall bladder disease, and was present in 33 per cent of cases operated for acute cholecystitis. Of all the cases, 75 per cent had symptoms typical of recurrent acute cholecystitis and chronic cholecystitis; only 12 per cent had no previous gall bladder history. A palpable gall bladder was present in 39 per cent of cases. Obstruction of the cystic duct was found in 93 per cent and perforation of the gall bladder was present in 24 per cent but none were free perforations.

Cholecystectomy was performed in all cases with a mortality rate of three per cent. Microscopic examination revealed massive necrosis, congestion, edema, hemorrhage, thrombosis, fibrosis, subintimal arterial edema and proliferation. Evidence of infection was found in 41 per cent of cases.

The authors believe that the treatment of choice is early operation and the operation of choice is cholecystectomy, although cholecystostomy may be advisable in certain selected cases. They further believe that cholecystectomy early in the course of recurrent acute cholecystitis or chronic cholecystitis would prevent many cases of gangrenous cholecystitis; since, in their series, 88 per cent had had previous attacks.

FRANK G. VAL DEZ

HEERSMA, J. R. AND ANNIGERS, J. H. Effect of cholecystectomy on fecal fat excretion in dogs. *Proc. Soc. Exp. Biol. Med.*, 69: 140 (Oct.) 1948.

The question was posed whether cholecystectomy, which converts the normal intermittent flow of concentrated bile into a

continuous flow of dilute bile into the intestine, would result in a defect in fat absorption. In 8 dogs studied both before and after operation, cholecystectomy produced no significant change in the daily excretion of fat or nitrogen.

H. NECHELES

VILLASEÑOR, M. S. Aspiration of amoebic liver abscess. *Rev. de gastro-enterol. de México*, 13: 293 (Sept.-Oct.) 1948.

Forty two cases of amoebic liver abscess were seen during the last three years. Emetine was used for five days before aspiration was considered. A needle having 1.5 mm. in caliber was used for the aspiration. In some cases, 2 or more aspirations were performed. Ninety eight per cent of the patients were cured with this treatment.

ALOYSIO FARIA

SCHRUMPF, C. A. Present fundamentals of some liver function tests. *Am. J. Dig. Dis.*, 15: 367 (Nov.) 1948.

A number of the liver function tests in current use are discussed, and the numerous limitations of the various tests for liver function are emphasized.

The author calls attention to the limitations of the bromsulfalein tests and of the qualitative van den Bergh reaction in the differential diagnosis of liver disease. He stresses the value of the galactose test in the differential diagnosis of jaundice and advocates a modification of the usual test in which the patient is given a combined dose of galactose and gelatin. In normal individuals this is not followed by appreciable rise in the blood sugar, although such a rise occurs in the presence of liver disease. The galactose-gelatin test was positive in 9 of 12 patients with acute hepatitis, and also in 3 of 7 patients with cholelithiasis.

With reference to the hippuric acid test, the author advocates an oral method and states that the intravenous technique is so sensitive as to seem unsuitable for the differentiation between hepatitis and obstructive jaundice. The value of the various flocculation tests is stressed and, of these, the author prefers the Takata reaction, although it is recognized that this is not specific for liver disease.

HENRY TUMEN

PANCREAS

BOCKUS, H. L. AND RAFFENBERGER, E. C. Acute pancreatitis. *N. Y. State J. Med.*, 48: 2252 (Oct.) 1948.

The severe form of acute pancreatitis is associated with necrosis. There is a milder form with abrupt onset which is called edema of the pancreas, subacute pancreatitis, acute transient pancreatitis, or interstitial pancreatitis. The etiology is unknown, but two factors occurring commonly are alcoholism and concomitant biliary tract disease. There is no consistent symptom complex. The initial pain is most commonly in the epigastrium. It may also occur in the lower abdomen, in the lumbar region, beneath the sternum, or in the left chest. The pain is often sharp and constant, but may be dull and intermittent. The radiation is usually to the left, and to the region of the first and second lumbar vertebrae. The differential diagnosis must include acute coronary occlusion, mesenteric artery occlusion, perforated viscus, acute pneumonitis, acute alcoholic gastritis, and acute appendicitis. In acute pancreatitis, the shocklike state is striking. Skin changes may appear as cyanosis of abdomen or limbs, and brownish discoloration or petechiae below the ribs posteriorly or on the buttocks. Since the diagnosis is rarely, if ever made clinically, blood enzyme studies are of greatest importance. If a hyperenzymemia exists, one may diagnose acute pancreatitis with certainty. Normal blood serum values do not exclude the disease, however. A blood calcium level below 7 mg. per 100 ml. is considered to be a bad prognostic sign. Profound changes may occur in the electrocardiogram in acute pancreatitis, such as inversion of the T wave and depression of the ST segment. The abnormalities in the electrocardiogram gradually return to normal and may be due to shock or diminution in concentration of serum potassium. The latter can occur because of Wangensteen drainage, prolonged vomiting and dehydration, or administration of excessive sodium ions.

Treatment should be conservative. The regime as employed by the authors consists of the following: (1) Relief of pain—morphine should be avoided because of its possible vagotonic action and demerol is the

analgesic of choice; (2) treatment of shock and dehydration by blood and plasma transfusions, and parenteral glucose solutions; (3) avoidance of hormonal stimulation of the pancreas by instituting Wangenstein suction to prevent HCl from reaching the duodenum; and (4) avoidance of nervous stimulation of the pancreas by withholding any drug which may stimulate the vagus. Atropine gr. 1/75 of 1/150 every 4 hours is of benefit. Calcium gluconate may be given if hypocalcemia is present.

In a series of 10 cases thus treated, 100 per cent recovery was obtained.

PHILIP LEVITSKY

MCDONOUGH, F. E. AND HEFFERNON, E. W.
Chronic relapsing pancreatitis. *Surg. Clinics N. Am.*, 733 (June) 1948.

This disease is characterized by recurring attacks of pain in the upper abdomen associated with disturbances of function of the pancreas and their sequelae. During the acute phase, the pain is usually severe, steady and prolonged, characteristically radiating to the back. It may be associated with other symptoms such as nausea, vomiting and diarrhea. Steatorrhea and creatorrhea are usually late signs in the disease. The disease occurs most frequently in the middle age group.

Examination during an acute attack may reveal epigastric tenderness and muscle spasm, moderate fever, slight jaundice and mild shock. Laboratory examination may reveal a glycosuria or a steatorrhea. The serum amylase and lipase are frequently elevated during an exacerbation but are usually normal between attacks. Roentgenologically, 50 per cent of cases show calcification of pancreas sometime during the course of the disease; pancreatic cysts are occasionally demonstrable. At surgery the pancreas appears hard and firm and may be edematous and contain calcified abscesses and cysts.

The medical treatment consists of treating the diabetes and steatorrhea if present, a dietary regime similar to that used with irritable colon, and analgesics for relief of pain. Surgical procedures include correction of biliary disease if present, and drainage of cysts and abscesses. Sometimes pancreatectomy and splanchicectomy are

employed for relief of pain. A typical case history of chronic relapsing pancreatitis with transient diabetes during acute phases is presented. A bilateral thoracolumbar sympathectomy apparently relieved this patient of his pain.

FRANK G. VAL DEZ

PARSONS, W. B. Radical operations on the head of the pancreas. *N. Y. State J. Med.*, 48: 2149 (Oct.) 1948.

Cancer of the pancreas is rarely recognized early enough to effect an operative cure. However if the disease is confined to the head of the organ, and jaundice appears early, then treatment may be undertaken before there is lymphatic invasion or extension into the superior mesenteric vein or retro-peritoneal tissues. In preparing the patient for operation, particular attention must be paid to the status of the heart, kidneys and liver. Any deficiency in the blood must be corrected. The operation consists of excising the cancer area en bloc with those structures whose blood supply would be impaired. The bile and pancreatic ducts must be anastomosed to the alimentary tract. Postoperative measures are directed toward maintenance of nutrition and restoration of normal fluid, protein and electrolyte levels. Overhydration as well as dehydration must be avoided. The mortality rate is high and death in most cases is not due to operative shock but to physiological disturbances which are unrecognized or are irreversible due to impaired liver and kidney function.

PHILIP LEVITSKY

WHIPPLE, A. O. A discussion of the lesions of the pancreas amenable to surgery. *J. Mt. Sinai Hosp., N. Y.*, 15: 123 (Sept.-Oct.) 1948.

Because of the serum amylase test, acute pancreatitis is diagnosed much more often but operated upon far less frequently than formerly. On the other hand, for neoplasms of the organ, partial and even total pancreatectomy is now being done in many of our surgical clinics in increasing numbers. In addition to the tumors, the lesions now amenable to surgical therapy are: (1) in subsiding acute inflammation with abscess formation; (2) in chronic inflammatory le-

sions with fibrosis of the organ and calcareous deposits in the duct system or more rarely in the parenchyma of the organ; and (3) for drainage of pancreatic cysts, but rarely for excision of the cyst. In the past 5 years, the mortality rate has been 15 per cent in 46 cases of acute pancreatitis as proved by delayed operation or autopsy. In the two previous 5-year periods, when operation was done as soon as the diagnosis was made, while the patient was still in serious shock, the mortality was 34 per cent. Severe intractable pain in chronic pancreatitis may be an indication for surgery when associated with morphinism. Duodenal intubation is an important aid in the differential diagnosis of obstructive lesions in the ampullary area due to common duct stone or neoplasm, chronic pancreatitis, carcinoma of papilla of Vater and carcinoma of the head of the pancreas. The use of the secretin test and mechoyl in diagnosis is also described. The majority of islet cell tumors of the pancreas are benign adenomas but a certain number are malignant. Because of the hypoglycemic episodes associated with these tumors, disorders, of the liver, adrenal, pituitary and thyroid glands and thalamus, must be ruled out. Surgery is definitely indicated and should not be delayed when the diagnosis of islet cell tumor is made. In malignant tumors of the pancreas of the ampullary area, the one-stage radical procedure is preferable to the two-stage method.

ALBERT CORNELL

RICHMAN, A. AND COLP, R. Subtotal gastrectomy in the treatment of chronic recurrent pancreatitis. *J. Mt. Sinai Hosp., N. Y.*, 15: 132 (Sept.-Oct.) 1948. The medical therapy of chronic relapsing pancreatitis has been of little avail in controlling the symptoms or in altering the course of the disease. The authors present such a case of pancreatitis of 14 years' duration. Following the development of a gastric ulcer, subtotal gastrectomy was done to remove the lesion and to alleviate the pancreatitis by interference with the secretin mechanism of pancreatic secretion. A dramatic cure resulted with disappearance of pain, steatorrhea and creatorrhea. Diminished gastric acidity and diversion of the

acid chyme from the duodenal mucosa into the jejunum account for the reduced amount of secretin. This results in a lessened quantity of pancreatic juice which then flows under decreased pressure through the ducts. Thus, distention of the ducts does not occur and pain is not experienced. The patient was able to gain weight and strength sufficient to allow him to return to work after 8 years of disability. Because of the dramatic relief obtained, the authors suggest the operation of subtotal gastrectomy for chronic relapsing pancreatitis.

ALBERT CORNELL

POPPER, H. L. AND NECHELES, H. Pancreas function tests. *Am. J. Dig. Dis.*, 15: 359 (Nov.) 1948.

The authors present a brief critical review of the older as well as more recent methods for diagnosing pancreatic disease. They conclude that while determinations of serum amylase and lipase are fairly reliable in the study of acute pancreatitis, they are of relatively little value in diagnosing other forms of pancreatic disease. It is recognized that secretin stimulation of pancreatic secretion combined with aspiration of the pancreatic juice by means of duodenal intubation is an extremely valuable method for the study of the pancreas, although the various technical problems involved make this procedure rather cumbersome for general use.

The authors have developed a method for studying pancreatic function which is based upon determination of the pancreatic enzymes in the blood, first, after moderate stimulation of pancreatic secretion by means of secretin and, second, by very active stimulation of the pancreas by the administration of secretin and mechoyl. It is thought that the first procedure is a test for obstruction of the pancreatic ducts and that the second is a means of recognizing secretory deficiencies of the pancreas.

HENRY TUMEN

BARRON, S. S. Significance of the beta granules in the islets of Langerhans of the pancreas. *Arch. Path.*, 46: 159 (Aug.) 1948.

The islets of Langerhans are composed of alpha and beta cells which have distinctive

staining characteristics with Gomori's stain. The beta cells contain numerous small particles, beta granules, which stain blue by this method.

In adenoma of the pancreas associated with hyperinsulinism, the cells contain beta granules. On the other hand, the pancreas of human diabetes is usually deficient in beta granules and this is the only recognizable abnormality. The significance of degranulation is not understood and the author instituted experiments to determine whether the beta cells could be degranulated by procedures which decrease the demand for insulin.

Best, Haist and Ridout showed that the insulin content of the pancreas of rats was reduced after subjecting these animals to fasting, after keeping them on a fat diet for a period, and after the administration of insulin. The author used groups of white rats and subjected them to the same conditions. The animals were killed at the end of the experimental period and the pancreas stained by Gomori's method. All three experimental procedures resulted in a diminution in the beta granules of the beta cells. Best and Haist showed a decrease in the insulin content of the rat pancreas by these procedures. The author concludes that since there is a direct correlation between the insulin content of the pancreas and the number of beta granules, the beta granules represent insulin precursors.

NATHAN SHAPIRO

ULCER

LEVIN, E., KIRSNER, J. B. AND PALMER, W.

L. Twelve-hour nocturnal gastric secretion in uncomplicated duodenal ulcer patients: Before and after healing. *Proc. Soc. Exp. Biol. Med.*, 69: 153 (Oct.) 1948.

The nocturnal gastric secretion was determined in a group of patients with uncomplicated active duodenal ulcer having distress, and in the same individuals during a period when the ulcer was healed and symptoms were not present. In patients with duodenal ulcer, the 12-hour nocturnal gastric secretion is usually unaltered with healing of the ulcer. The average 12-hour nocturnal gastric secretion of patients with active ulcer is not significantly different

than in patients with healed duodenal ulcer. Twelve-hour nocturnal gastric secretion in patients with healed duodenal ulcer without symptoms is significantly greater than that of normal healthy individuals.

H. NECHELES

SURGERY

HIGGINSON, J. F. AND CLAGETT, O. T.
Gastric resection: The Schoemaker-Billroth I operation. *Surgery*, 24: 613 (Oct.) 1948.

The Schoemaker modification of the Billroth I operation permits more extensive resection of the lesser curvature of the stomach than other similar operations. After resection, the lesser curvature margin of the stomach is closed, producing a tube-like stomach with a stoma at the greater curvature aspect. This stoma is then utilized to produce an end-to-end gastro-duodenostomy. While the advantages of this type of anastomosis are similar to those obtained following a Hoffmeister-Polya, i.e. less postprandial distress and less difficulty in maintaining body weight, the Schoemaker-Billroth I is more physiologic and more productive of post-operative comfort.

The operation was done in 95 cases, all except three being gastric lesions: gastric ulcer—37, carcinoma of the stomach—35, chronic gastritis—4, gastrojejunal ulcer—3, multiple polyposis of the stomach—1, lymphosarcoma of the stomach—1, inflammatory cyst of the stomach—1; duodenal ulcer—3. Definite leakage at the site of anastomosis occurred in 2 cases. One of these patients died on the ninth postoperative day; in the other, the fistula healed spontaneously. Two hospital deaths (2.1%) occurred, only one of which (above) was due to surgery. Sixteen cases (16.8%) had significant post-operative gastric retention, the criteria being the vomiting of more than 100 cc. fluid during the first 48 hours. Five cases suffered retention more than three days.

Despite the superior technical advantages of this type of operation, the procedure is limited almost entirely to gastric lesions because of previous contracture deformity in duodenal ulcer.

A. I. FRIEDMAN

BEAL, J. M. Diaphragmatic hernia following subdiaphragmatic vagotomy. A case report. *Surgery*, 24: 625 (Oct.) 1948.

A case of diaphragmatic herniation following a successful subdiaphragmatic vagotomy for peptic ulcer is presented. Ten days post-operatively, a follow-up gastrointestinal X-ray examination revealed a pouch arising at the esophagogastric junction ascending through the esophageal hiatus (paracophageal). The patient had very insignificant complaints, but was operated on six months later for transthoracic repair of the hernia.

Paracophageal herniation may occur by relaxation of the hiatus due to spreading of the longitudinal fibres of the diaphragm in the delivery of the lower esophagus. Prior to this case, suture of the mediastinal opening made for subdiaphragmatic vagotomy had not been performed routinely due to technical difficulties. In the future, closure of the esophageal hiatus is recommended whenever possible.

A. I. FRIEDMAN

PATHOLOGY

POPPER, H. Significance of agonal changes in the human liver. *Arch. Path.*, 46: 132 (Aug.) 1948.

There is frequently considerable difficulty in correlating histologic changes in the liver with clinical manifestations of liver disease. In many instances the functional significance of morphologic alterations cannot be evaluated. The problem is greater as a result of premortal, agonal and postmortal changes when the histologic studies are based on autopsy material. Recent study of liver biopsy material has served to emphasize these changes and the rapidity with which they may occur.

A study was made in order to clarify the nature and extent of agonal changes in the liver: (1) The histologic picture as seen in autopsy material was compared with that seen in biopsy specimens without any attempt to study the same liver in premortal and postmortal material. (2) Premortal and postmortal histologic comparisons were made in rare cases where a biopsy specimen was obtained shortly before death. (3) Livers of healthy persons who died instantaneously were compared with those of persons

who died suddenly but with an interval longer than 10 minutes elapsing between the onset of the injury or disease and actual death. The changes in each group are discussed in detail.

A comparison of biopsy and autopsy specimens of hepatic tissue revealed cytoplasmic changes due to the absence of glycogen from the latter. Such comparisons also demonstrated that the perisinusoidal tissue spaces are usually closed in biopsy specimens and open in autopsy material. Comparison of biopsy specimen taken from a liver a few hours before death and an autopsy specimen of the same liver shows that striking dissociation of liver cell cords may occur in the agonal period. This is rarely seen in biopsy specimens. In autopsy specimens of persons dying instantaneously the tissue spaces are obliterated, while in specimens obtained after a 10-minute or longer agonal period, they may be wide open.

NATHAN SHAPIRO

PHYSIOLOGY: SECRETION

KIRSNER, J. B., LEVIN, E., AND PALMER, W. L. Failure of an extract of pregnant mares' urine to influence gastric secretion in man. *Proc. Soc. Exp. Biol. Med.*, 69: 108 (Oct.) 1948.

A preparation of extract of the urine from pregnant mares, termed "Kutrol" is described as entirely devoid of estrogenic or gonadotropic activity, highly soluble in water and manifesting an acceptable degree of antiulcer activity when assayed on the Shay rat; its nature is not known. Bercovitz *et al.* have reported results in the treatment of chronic duodenal ulcer with doses of 0.6 g. of this substance by mouth daily in divided amounts.

Twelve patients, 10 with active duodenal ulcer and 2 with gastric ulcer, were studied. Continuous gastric suction was maintained. In 4 patients, the 12-hour nocturnal gastric secretion was measured before and approximately 2 hours after the administration of the extract via the stomach tube. In 4 patients, gastric suction was continued for 36 hours; after 16 or 17 hours, 7.1-7.5 g. of Kutrol were introduced into the stomach via the Levine tube. Four other patients were

studied in an identical manner, but received 7.5 g. of an "inactive" material as control.

Kutrol, in quantities as large as 7.5 g., does not decrease the volume, free acidity, or output of hydrochloric acid in the 12-hour nocturnal gastric secretion or in the continuous 36-hour secretion of patients with peptic ulcer.

H. NECHELES

PHYSIOLOGY: MOTILITY

LOOMIS, T. A. Response of the duodenum to morphine. *Proc. Soc. Exp. Biol. Med.*, 69: 146 (Oct.) 1948.

Acute experiments were carried out on mongrel dogs anesthetized with sodium pentobarbital. Jackson's internal organ apparatus was sutured to the mucosal surface of a segment of duodenum which contained a small rubber balloon within its lumen. The intestine was replaced in its approximate normal position and the abdominal incision was sutured.

Tachyphylaxis of the intestinal musculature to intravenously injected morphine was demonstrated. The most consistent response of the circular muscle of the duodenum to morphine was an increase in muscular activity, elevation of the tonus level with increased frequency and amplitude of the normal spontaneous tonic contractions. The most frequent response of the longitudinal muscle was either a decrease or an abolition of activity, depression of tonus, decreased frequency and amplitude of the normal spontaneous tonic contractions. The type of response of the duodenum to morphine was independent of the original state of tonus and independent of the dose, between 0.01 and 1.0 mg. per kg.

H. NECHELES

METABOLISM AND NUTRITION

WERNER, S. C. Problems of parenteral Nutrition. *Am. J. Med.*, 5: 749 (Nov.) 1948.

Almost all the essential materials for adequate parenteral nutrition are in use today. Parenteral feeding can be used to supplement limited food intake by mouth or to replace food entirely when the oral route is not available. The indications for paren-

teral therapy are: (1) disorders of ingestion; (2) disorders of absorption; (3) disorders of utilization; and (4) hemorrhage; dehydration and shock from any cause. Nutritional factors in parenteral therapy include electrolytes, carbohydrates, fat and protein. The administration of electrolytes should be carefully controlled because excesses of sodium chloride may cause edema, transient increases in blood volume and consequently congestive failure in precariously compensated patients; excess of potassium is even more poorly tolerated. Dextrose in 5 and 10 per cent solutions are customarily used as a carbohydrate source. The use of fat emulsions for intravenous administration is still in the experimental stage.

Proteins intravenously affect osmotic pressure and blood volume; human plasma, whole blood, or serum albumin are the agents used. Protein hydrolysates, for which casein is the most frequently used parent protein, and synthetic mixtures of amino acids furnish the precursors of protein for synthesis by the body. The commercial product for intravenous use is limited by tolerance and speed of administration. The liver is the principal organ concerned with deamination of amino acids and the synthesis of serum albumin. Liver insufficiency with hypoproteinemia is best corrected with whole blood plasma or human albumin. Though blood and plasma are superior in controlling nitrogen balance, oral and parenteral amino acids are essential for the maintenance of normal liver function. Carbohydrate is essential for protein nutrition because its caloric contribution spares nitrogen. Complications from the use of parenteral fluids include venous thrombosis, vomiting, shock-like responses, transfusion reactions, homologous serum jaundice, and cardiac and renal failure.

MICHAEL W. SHUTEIN

ELMAN, R. Amino acid mixtures as parenteral protein food. *Am. J. Med.*, 5: 760 (Nov.) 1948.

The literature for the years 1945, 1946 and 1947 is summarized on the use of amino acid mixtures as a parenteral protein food. The generic terminology, amino acid mixtures, is preferable because it includes the pure

crystalline amino acids and the hydrolyzed protein.

An amino acid mixture prepared from pure crystalline material was first injected in 1940 by Shohl and Blackfan. Numerous amino acid mixtures for parenteral use prepared from protein hydrolysates have been prepared and studied. Amino acid mixtures may contain impurities and vary in pH and electrolyte composition. Reactions following intravenous injection of amino acid mixture are nausea and vomiting, chills and/or fever, headache, dyspnoea, precordial and lumbar pain, anorexia, vertigo and weakness. Crystalline mixtures of amino acids with glycine are far better tolerated than hydrolysate mixtures.

Observations made on the metabolism of intravenously administered amino acid mixtures reveal that the peptides of Amigen appear to be less readily utilized by the tissues and more poorly retained by the kidneys than pure amino acids. Nitrogen balance studies also revealed that, at low levels of intake, a mixture of crystalline amino acids maintained nitrogen balance better than in a similar level of Amigen, whereas at a high level of intake the reverse was true. The nitrogen balance was just as good with the intravenous as with the oral route. Physiologic effects, following amino acid mixtures intravenously, were noted in the motility and tonus of the intestine and an increased utilization of glucose when the latter was added. Clinically, parenteral amino acid mixtures accelerated convalescence.

MICHAEL W. SHUTKIN

PHARMACOLOGY

KRAMER, P. AND INGELFINGER, F. J. Use of antispasmodics and spasmodics in the treatment of gastrointestinal disorders. *Med. Clinics N. Am.*, 1227 (Sept.) 1948.

It is desirable that antispasmodics be effective when administered orally; they should furthermore be non-habitforming, inexpensive, and their action should be extended while producing only minimal toxic effects. The ideal antispasmodic is not yet available. Antispasmodics depress motor function of the smooth intestinal musculature either directly, or through anticholinergic or adrenergic

action. Most effective are the belladonna alkaloids which possess anticholinergic properties. The largest dose barely producing side reactions is considered optimal; while this dose will depress normal gastrointestinal motility, severe disorders require larger doses. Although tincture of belladonna contains alkaloids other than atropine, no significant difference exists between their antispasmodic properties. In effect and side reactions levorotatory hyoscyamine (bellafoline) is similar to atropine. Extreme and unpredictable side reactions preclude routine use of scopolamine. Rapid but only transient spasmolytic action is obtained through medication with nitrites or with papaverine. As spasmolytics, adrenalin and amphetamine are merely of theoretical significance. Synthetic antispasmodics, such as trasentine and syntropan, affect the intestinal musculature directly, produce minimal side effects, but have only limited spasmolytic action. Tetraethylammonium seemed to be in no way superior to atropine. Conditions requiring the use of spasmodics, such as megacolon, paralytic ileus, stubborn constipation, or postvagotomy complaints, are not very frequently encountered. The cholinergic compounds (mecholy, doryl, and urecholine) as well as the anticholinesterases (physostigmine, prostigmine, and di-isopropylfluorophosphate) are evaluated. Urecholine was found most effective in the treatment of gastric retention following vagotomy. Pituitary extracts produce direct stimulation of the smooth muscles of the gastrointestinal tract.

L. T. ROSENTHAL

MISCELLANEOUS

KARDON, S. C. Anion exchange resins in the treatment of heartburn during pregnancy. *New Eng. J. Med.*, 239: 575 (Oct.) 1948.

Heartburn, according to modern physiologic concepts, is due to the regurgitation of gastric contents into the distal esophagus distending the sensitive neural endings. The distention is enhanced by the intermittent spasm of the cardiac sphincter. Prostigmine, shown clinically and experimentally to increase isoperistaltic contractions in the gastrointestinal tract, has afforded satis-

factory relief from pyrosis during pregnancy. Anion exchange resins, though empiric and unphysiologic agents, have offered as good relief as that obtained with cholinergic substances.

After summarizing the changes in the stomach and its physiology during pregnancy, the author describes his results. The administration of anion exchange resin orally, for the relief of annoying heartburn in pregnancy, has resulted in rapid relief of this symptom in 88 per cent of treated cases. This salutary result is at least comparable to that reported with prosthigmin. Cholinergic drugs have been used to excellent advantage in heartburn of pregnancy in accordance with the neuromuscular dysfunction theory now accepted by most physiologists. Yet this therapy appears to be no more effective qualitatively or statistically than anion exchange resins. This consideration suggests that there is still much to be explained in the etiologic picture of heartburn during pregnancy. The reports of relief obtained from the administration of such substances as yeast, thiamine chloride and nicotinic acid merely add to the confusion. Between 8 and 20 per cent of the failures to obtain relief with any medication may be attributed to the presence of an occult diaphragmatic hernia that is reduced spontaneously postpartum.

The fact that 88 per cent of the patients treated for heartburn with resin obtained complete relief makes it very unlikely that the mechanism is psychogenic. Rather, Bartlakowski has reported that 70 per cent of esophagi studied microscopically showed islands of gastric-secreting mucosa in the distal segment, and it is suggested that these gastric glands secrete sufficient acid and pepsin locally to complement that derived from the reflux of gastric juice, and sufficient to discharge the sensory nerve endings of the lower esophagus which have been primed by mechanical distention demonstrated to be present. The pepsin-inactivating role of the anion exchange resins employed in this study

may play an undetermined part in the effectiveness of this medication. The resin is recommended because of its value in control of heartburn during pregnancy, its freedom from toxicity and its economy.

ANTHONY M. KASICH

SHOENFELD, H. B. Tropical diseases of the gastrointestinal tract in veterans. *N. Y. State J. Med.*, 48: 2133 (Oct.) 1948.

Amebiasis is the most important of the tropical diseases seen in veterans. It may exist in an asymptomatic form for a long time. About 10 per cent of veterans in New York City harbor *E. histolytica* in the stools as compared to 5 per cent of the general population. About one-half of the cases do not complain of diarrhea. Abdominal pains may be present, with or without diarrhea. Blood in the stools is present in about 16 per cent. In about 20 per cent of cases the symptoms are entirely constitutional. Hepatic involvement occurs in about 5 per cent. This may lead to simple hepatitis or abscess. No case can be considered as negative, unless warm, purged stools are examined.

Helminth infestation is not an important disease among veterans. The common forms are hook worm, ascaris and trichiuris. They are easily diagnosed and respond quickly to treatment.

Many cases of schistosomiasis occurred during the Leyte campaign of 1944. Most of them were detected and treated successfully. Cerebral and hepatic complications were seen. Repeated stool examinations may be necessary in order to detect the ova. Few cases of giardiasis were encountered, probably because the troops were given atabrine as a malaria suppressive.

Sprue is one tropical disease that is often undiagnosed in its early stages. When the disease is well-marked by soreness of tongue, macrocytic anemia, disturbance of intestinal motility, fatty diarrhoea, it is easily recognized. Treatment consists of low fat, high protein diet and injections of crude liver extract.

PHILIP LEVITSKY

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PRESIDENTIAL ADDRESS: TRENDS IN GASTROENTEROLOGY*

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The obligation to make this address gives me an opportunity which I have long desired to discuss trends in the field of gastroenterologic research and practice. Since its inception in 1897 this Association has provided a forum for the discussion of the many new advances in medicine in general and gastroenterology in particular, as they have been brought to the attention of our members. The membership of this Association, consisting of workers in many different fields but all interested in the problem of digestion and nutrition has provided an ideal background for discussion of these problems. As one who has has missed but one meeting of this Association since 1911, who has been a member since 1920 and who has devoted his whole time for thirty-four years to gastroenterologic practice and to teaching at undergraduate and graduate levels, I feel qualified to discuss the trends in this field, even though there will probably be many who will disagree with my opinions. In presenting my thesis I shall endeavor to avoid all personalities.

Before the advent of the American Gastroenterological Association a gastroenterologist was a man with a stomach tube and a couple of bottles of indicators who prescribed alkalis or acids according to the findings on titration of the contents pumped out of the stomach. In 1897 a group of men interested in improving the status of gastroenterology and realizing the importance of accurate knowledge to guide the clinician in caring for disease of the alimentary canal, laid the foundations of this Association. In his presidential address last year Bockus pointed out the important role which has been played by this Association and its members in the advancement of medical research. The vision of our founders has been justified beyond any conception they may have had of its possibilities.

In general, the trends in gastroenterology have been made evident in the proceedings of the Association. In the early days, an exchange of ideas between clinicians, physiologists and pathologists laid the foundations for future con-

* Presented at the annual meeting of the American Gastroenterological Association, June 4, 1949, Atlantic City, New Jersey.

structive work in our field. Methods of diagnosis were discussed, treatments based on physiology were recommended and structural lesions began to be understood. There was for a while much prating about intestinal stasis and toxemia and later considerable time was devoted to discussing focal infection. With the advent of the Roentgen ray first the physiologist and then the clinician made use of this improved medium for the study of gastroenterologic form and function. The pioneer roentgenologists became members of our Association and demonstrated the value of their researches in successive reports. The esophagoscope and gastroscope were introduced making important additions to our diagnostic methods. Surgery was becoming more daring and our surgeons and internists consumed much time in discussing the relative merits of their methods of treatment. As the large clinics began to accumulate large series of gastroenterologic cases, statistical studies began to attract attention. Physiologic research in gastroenterology became the order of the day and fractional methods of removal of gastric and duodenal contents, studies of biliary and pancreatic function and of the hormones and investigation of animal and human gastrointestinal motility resulted in more positive diagnosis and more rational therapy. Allergic reactions in the gastrointestinal tract were discussed. The clinical pathologist began to contribute more and more to our armamentarium. Stools, at first merely tested for occult blood and acidity, were studied for chemical and cytological evidences of disease and for parasites and ova. Bacteriologic researches began to assume importance. The making of cultures, serological and agglutination tests, vaccines, sera and bacteriophages became routine. The relation of anemias to the gastrointestinal tract was studied, chemical examination of the blood and other body fluids assumed importance and researches in nutrition brought new contributions to our meetings and new members into our fold. The interrelationship between gastrointestinal function and disease and the circulatory, respiratory, genito-urinary and nervous systems was stressed and workers in these fields were invited to join us. Cooperative projects in gastroenterologic research were carried out and our present Committee for the Study of Peptic Ulcer, now doing a monumental piece of work, promises to be but the forerunner of other similar projects in other fields of research. As a result of all these influences we have reached a point where at this meeting one-half of our papers constitute reports of research work, mostly in the realm of gastrointestinal physiology, but also including research in the neuropsychiatric field as related to gastroenterology and at this meeting for the first time in the field of radio-isotope studies, which promise to revolutionize the whole practice of medicine within the next decade. One-third of our papers at this session are devoted to clinical research and less than one-third to diagnostic methods and the newer methods of therapy.

Education has always received our attention. The publication of transac-

tions, followed by experiments in publishing a journal culminated in the production of "Gastroenterology", one of the best journals devoted to a specialty field and wielding a powerful influence in the guidance of medical opinion and practice. Postgraduate education in our field has been fostered by the establishment of fellowships and by the formation of the sub-specialty board of gastroenterology as a part of the American Board of Internal Medicine, which, by setting up standards for the training of gastroenterologists and by certifying those who qualify as specialists, is creating a demand for better postgraduate training. We now have a committee which is making a study of facilities for such training. Our Board has an advantage in that, by requiring that all candidates for its examinations must be certified in Internal Medicine in addition to showing evidence of adequate training in gastroenterology, there is a longer period of preparation before certification is granted. However, we are suffering from the fault of all specialty boards in that young men, anxious to qualify as soon as possible as specialists, tend to place much more stress on formal, more or less didactic training than on practical experience in their special field. Many of these rapidly created specialists later find that they would prefer some other kind of practice and begin to specialize in an entirely different branch of practice. Then, even though they are no longer conversant with the advances in their original specialty, they are still certified as experts in it, which creates embarrassment not only for themselves but also for the Boards which certified them. I believe that the specialty boards may be obliged to consider the advisability of certifying candidates at first in some temporary way, similar to our associate membership, and then after a period of years, during which the candidate has demonstrated real leadership in his field, to grant a full certification. And I am heartily in favor of the trend toward requiring general practice preliminary to specialty training. It should also be stressed that some practical experience in pathology, roentgenology and surgery is particularly valuable in the training of a gastroenterologist.

In the field of *medical literature* in general we are today suffering from an overproduction of papers. The requirements for appointments to medical schools, hospitals and clinics and for admission to medical societies and to specialty board certification all include the publication of papers, thus encouraging much writing that is of little or no value or but a duplication or rearrangement of previous material. The medical practitioner has not the time to read all of these papers, so we have developed the abstractor, who, also pressed for time, frequently misses the really essential points brought out by the writer. Other authors in reviewing the literature, often quote only from these incomplete or incorrect abstracts and may use only those which appear to agree with their own views. And in many instances writers will not take the time to review older literature which contains original contributions on subjects

which they bring up as originating with themselves. Many authors feel that statistics are the most important consideration in preparing a paper, and we see many pages of such statistics, often irrelevant to the subject the value of which they are supposed to enhance, and all too frequently subjected to the same distortion for which all statistics are notorious. We can only hope for the utopian era when only those who have something new to report or whose long experience qualifies them to evaluate what has gone before will write brief, succinct articles for fewer medical journals.

In the field of *investigation* the members of our group have made many of the most outstanding contributions to modern medical thought and have exerted a powerful influence on the diagnosis and rational scientific treatment of gastrointestinal ailments. Investigative work such as is being reported upon at this meeting, with a practical bearing on problems in gastrointestinal disease, should be encouraged. And too much cannot be said in favor of such studies as those made on "Tom" and other patients with fistulous openings of various kinds by investigators who are qualified to evaluate their findings.

In the realm of *diagnosis* efforts are constantly being directed to simplifying and shortening the methods used. While this may seem of importance to the laymen who are our patients it is well to remember that most of our aids to diagnosis are of necessity time-consuming. No questionnaire filled in or merely checked by the patient will take the place of a careful history taken not by a nurse or junior assistant but by the experienced clinician himself. No cursory laying on of hands will take the place of a complete and thorough physical examination, not neglecting the insertion of the finger into the rectum. No passage of a stomach tube by a nurse and examination of aspirated contents by a technician, when he gets around to it, will give the information which can be obtained by the specialist in passing the tube himself and studying the aspirate in his own laboratory. No two minute fluoroscopy and snapping of a few films by a technician, no speeding up of motility by artificial means, no injection of barium into an already filled colon, no acceptance of the roentgen diagnosis of some unknown roentgenologist will take the place of an adequate study by an experienced roentgenologist, who has had years of experience in following his patients to the operating room, the follow-up clinic or the autopsy and who will take the time to go over his films with the clinician who is himself experienced in interpretation. The failure to make a complete gastrointestinal roentgen study because esophageal obstruction, biliary calculi, peptic ulcer or a colonic lesion have been found, often results in tragic errors of diagnosis. Notwithstanding the recommendation of hurry-up techniques, endoscopy of the rectum and sigmoid, the esophagus or the stomach cannot be hurried and often must be repeated to get results. Repeated and prolonged stool studies are required for determining the presence or absence of parasitic infestation.

Cytological studies, including the newer ones for carcinoma cells, take much time and need repeated examinations. Liver disease is not diagnosed from reports of a few function tests performed by a technician, and we must remember that the making of only a gastroenterologic study in a patient with gastrointestinal symptoms as is so often done today, is bad practice, often resulting in the overlooking of lesions elsewhere having an important bearing on diagnosis, treatment and prognosis.

Psychosomatic medicine is endeavoring to take over the field of gastroenterology. Study and treatment of patients with peptic ulcer and ulcerative colitis is now a part of the curriculum of psychiatric courses in medical schools. While the effect of acute psychic trauma on gastrointestinal function is easily demonstrable, the theoretical contention that repeated and continuous trauma will produce chronic organic disease fails to take into consideration the phenomena of conditioned reflexes and is not in accord with the facts as observed by experienced clinicians in the gastroenterologic field. In patients with ulcer or ulcerative colitis the lesions can be observed to heal while the supposed psychic influences are still operative, and following such clearing up of the lesions, the patients' psyche will improve to such an extent that the nervous symptoms can be postulated as having been caused by the disease, not vice versa. No experimental work has as yet demonstrated the production of more than functional changes by purely psychic influences. While much good has been accomplished by emphasizing the great value of the psychiatric approach to the treatment of all gastrointestinal ailments, it is to be feared that the present overemphasis upon this phase of medical care will produce a harmful reaction. When previous waves of psychosomatic "cures" were exploited to unjustifiable extremes, as in the case of disciples of Mesmer, Mary Baker Eddy, and Coué, the reaction resulted in years of neglect of the psychologic care which we know is of such value in all chronic cases.

In the realm of *treatment* gastroenterology is at present in a deplorably weak position. There is too much difference of opinion in regard to even the basic principles underlying what after all is the ultimate purpose of medical practice, the treatment of the ill patient. Too many clinicians are still content to treat symptoms instead of treating the patient, his illness and the causes of his illness. The many advertisements of new drugs, which keep our medical journals in circulation, which support our medical meetings and which consume so much of our time in reading and in being interviewed by detail men, stimulate the excessive use of these drugs. Our patients, who are still imbued with the belief that there is a panacea for every ailment, encourage us to use drugs even when they are unnecessary. I find it difficult to convince patients that, except in specific diseases curable by specific medication, no medicines are required. Usually they have been previously given drugs either frankly as placebos or on

the basis of symptomatic treatment. Sedatives, antispasmodics and antacids are thus often used needlessly and to excess, usually doing more harm than good. Liver, iron, vitamin and hormone preparations too often parenterally administered are favorite prescriptions and in recent years sulfonamides and antibiotics, as soon as they appear on the market are used indiscriminately in any case suggesting even possible infection. We are in need of more papers emphasizing that drugs should not be used except where specific indications for their use are recognized.

Removal of so-called *focal infections* had a tremendous vogue twenty-five years ago, but when too much was expected from too little thoroughness in the eradication of all foci of infection it was abandoned. The opponents of removal of these important factors in the etiology of so many diseases, not being able to demonstrate actual migration of bacteria from a focus to a diseased area, and failing to realize that absorption of the products (described now as histamine-like substances) produced at these foci might be the real cause of trouble, have made many clinicians almost afraid to advocate such prophylactic measures. I am shocked when patients who have previously been treated by clinicians of high repute open their mouths and disclose deeply carious and pyorrheic teeth, cryptic tonsils oozing pus and purulent discharges adherent to the pharyngeal walls and who describe greenish vaginal discharges which had been completely ignored. It would seem as if the cleaning up of any such areas of infection should be a part of the treatment of any patient, regardless of whether they are thought to be the specific cause of the disease for which the patient is being treated.

Dietetic treatment, so important in the field of gastroenterology, has ever varied according to the trend of the times. Successive theories in regard to etiology have produced such one-sided unbalanced diets as high fat and fat-free, high and low carbohydrates, high and low protein, salt-free, low-cholesterol and other freak diets. It should be kept in mind that the ideal diet is one which contains a proper balance of all ingredients, an adequate vitamin and mineral content and sufficient water and residue. Too many patients are being fed parenterally when they are perfectly able to eat their foods. Too many are being given amino-acids, the more refined successor to peptonized milk, by mouth, when protein can be digested, as in ulcer. There is no advantage in restricting fats and prescribing fatty acids as medicine for biliary tract drainage, when we know the value of fats in the diet in accomplishing this end. There is no reason for avoiding roughage, or "smoothage" as it is now called, and prescribing strained "baby" foods when there is no obstruction which would prevent its passage. There is frequently good reason for restricting foods which a patient knows do not agree with him or to which he has been shown to be allergic. While a diet containing adequate vitamins will obviate the necessity

for prescribing vitamin concentrates, it must be remembered that previous vitamin deficient diets may call for such additions in order more rapidly to restore vitamin balance. The trend toward using only one vitamin or one group of vitamins because the clinician feels there is a deficiency of only that one does not take into consideration the fact that vitamin deficiencies are practically always multiple and are usually accompanied by mineral and other dietary deficiencies. Transfusions, valuable as they are, should not be given indiscriminately. We should bear in mind that even with the most careful precautions, they are not without danger.

Our *surgical brethren*, with the aid of proper pre and post operative care, improvements in anesthesia and truly marvelous refinements in technique are so confident of their ability to perform miracles, that we are wondering how far they will go in removing and rearranging our gastrointestinal tracts. The advances in esophageal surgery promise to cure some cancers and to provide palliative relief in many cases, but I fear that in their enthusiasm too many surgeons are operating for functional conditions which could be better treated medically. Cancers in organs like the pancreas, formerly considered inaccessible, are now removed with comparative safety, but long-range cures are yet to be reported. In the treatment of ulcer and ulcerative colitis, our surgeons are still much at sea. After successive surgical attacks on ulcer by means of gastroenterostomy, plastic operations, progressively more drastic partial gastrectomies we have been observing a mass experiment on humans in the psychosomatic surgical operation of so-called vagotomy, and when we are told by our neuro-surgeons that stimulation of areas eight and nine in the orbito-frontal cortex of monkeys stimulates acid secretion in the stomach we must be fearful that orbito-frontal lobotomy will soon be advocated as the real scientific cure for ulcer. Too many clinicians and surgeons seem to have forgotten that an uncomplicated ulcer heals spontaneously and rapidly and I see too many patients who have undergone useless surgical attacks. In ulcerative colitis, the ultimate in surgical treatment today is colectomy, and the permanently ileostomized patient is described to us as a glamorous lothario, who not only may marry but actually propagate. Would that surgery be confined to removal of cancers and the treatment of complications of other gastrointestinal diseases!

I hope that my rather rambling remarks on so many subjects will not be construed as personal affronts to some whom I have had the presumption to criticize, but that they will be considered as an effort, inadequate as it may prove to be, to stimulate thought in the direction of simplifying and clarifying our efforts at healing the gastrointestinal invalid.

CARCINOMA OF THE PANCREAS, A CLINICAL AND PATHOLOGIC STUDY OF SEVENTY-FIVE CASES

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INTRODUCTION

Carcinoma of the pancreas is frequently seen in any large hospital, as it accounts for six per cent of cancers of the abdominal organs. With improvement in diagnosis, and more frequent exploratory operation it is hoped that an increasing number of these cases may be successfully operated before the tumor has invaded surrounding organs or produced metastases.

During a ten year period seventy-five cases of carcinoma of the pancreas came to necropsy at the Cook County Hospital. A clinical and pathologic study of these cases reveals a number of significant findings which are of value in diagnosis. An early diagnosis of pancreatic malignancy has become more important since the recent advances in the surgical treatment of these tumors. Every available clinical and laboratory aid must be utilized in the early diagnosis of the disease.

The possibility of carcinoma of the pancreas must be considered when a patient presents a history of abdominal pain (which is not due to peptic ulcer, gallstones or renal colic) associated with a progressive and rapid loss of weight, with or without jaundice.

The old concept of a painless progressive jaundice as the typical symptom-complex of pancreatic carcinoma must be forgotten, as most patients do have pain, and many do not have jaundice. We shall see that in this series of 75 cases only 37 tumors occurred in the head, 12 in the body, 16 in the tail, 8 in the body and tail, and 2 in aberrant pancreatic tissue. Jaundice developed in only one-half of these cases.

In the absence of jaundice the diagnosis is more difficult and we must depend upon a careful history of the type of pain, weight loss, x-ray findings of displacement or compression of the stomach or colon, a palpable mass, disturbance of sugar metabolism, and blood lipase and amylase studies. Exploratory laparotomy must be performed more frequently in suspected cases if we are to diagnose them in the operable stage.

In the presence of jaundice we are usually confronted with the problem of differentiating between surgical or obstructive and medical or hepatic jaundice. This is now possible with a great degree of accuracy.

In the separation of medical from surgical jaundice at least two positive tests are necessary to establish liver cell damage, but only one to recognize

marked bile flow interference (Popper and Steigmann¹). The laboratory tests of value are (1) cephalin-cholesterol flocculation, (2) thymol turbidity, (3) albumin/globulin ratio, (4) cholesterol ester/cholesterol ratio, (5) urinary urobilinogen, and (6) serum alkaline phosphatase. In some cases the bromsulfalein retention and hippuric acid synthesis may be added.

In many cases of jaundice bile flow interference and liver cell damage are associated. Popper and Steigmann found this in 60 per cent of cases of surgical jaundice, and in 26 per cent of cases of medical jaundice.

AGE AND SEX DISTRIBUTION

The highest incidence of cancer of the pancreas occurred in the sixth decade. There were 25 cases between the ages of 50 and 59. There were only six cases below age 40, and two were above 80 (Table 1). There is a preponderance in

TABLE 1

20-29.....	1
30-39.....	5
40-49.....	10
50-59.....	25
60-69.....	15
70-79.....	17
80-89.....	1
90-99.....	1

the male sex. Fifty-nine were males and sixteen females, a ratio of 3.7 to 1. Negroes are as frequently affected as whites. There were 53 whites and 22 negroes. This represents the ratio of white to colored admissions to the hospital.

SYMPTOMS

The duration of symptoms was recorded in 64 of the 75 cases. It varied from four weeks to two years. The average for this series was six months. In five patients the duration was given as two years. Levy and Lichtman², in 1940, reported 19 cases of carcinoma of the body and tail of the pancreas, two of which originated in pancreatic cysts with symptoms for two and one-half and three years.

The most frequent symptoms and signs in carcinoma of the head of the pancreas are weight loss; icterus with acholic stool; pain in the epigastrium, often radiating to the back and less severe in the upright position; a palpable tumor; enlarged liver; ascites; enlarged gallbladder; and constipation. In carcinoma of the body and tail jaundice is usually absent, making the diagnosis more difficult.

Pain was the chief complaint in 57 of the 65 cases in which a history was obtained. The pain was abdominal in 37, epigastric in 18, lumbar in 15, and

thoracic in 4. In 14 patients the pain was both abdominal and lumbar or thoracic. In 7, the pain was chiefly in the right upper quadrant, in 5 in the left upper quadrant. In 3, the pain was localized in the right kidney region, with radiation along the course of the ureter.

Pain is present in about 85 per cent of cases of pancreatic malignancy and is a very important and early symptom. In 95 of 109 cases reported by Rienhoff and Lewis³ pain was a prominent feature. It is the presenting complaint in three-fourths of all cases. The pain may be mistaken for spondylitis, intercostal neuralgia, calculus, or diaphragmatic pleurisy.

The pain may radiate from the epigastrium to the back, or to the right or left upper quadrant, or downward toward the groin. It may simulate gallbladder disease or penetrating peptic ulcer. An important characteristic of pancreatic pain is the variation in intensity with change of position. Lying usually increases the pain, hence many patients prefer to sit or lean forward. They may lie with the body curled, on the right or left side. Relief of pain by change of posture is suggestive of pancreatic tumor. The pain may be paroxysmal, without relation to the intake of food. It is often dull and boring.

The severe abdominal, lumbar, or thoracic pain may be the only symptom for weeks or months. It is frequently combined with nervous manifestations, such as depression with crying spells, anxiety, and insomnia. Some patients are diagnosed as psychotic, until the correct diagnosis is made.

A patient whom one of us (A. A.) saw recently was under observation for four weeks in a large clinic with a diagnosis of psychoneurosis. An x-ray study revealed an indentation on the greater curvature and posterior wall of the stomach. Under fluoroscopic examination a mass was palpable in this region. A diagnosis of carcinoma of the tail of the pancreas was made and confirmed at operation. Films taken a month earlier were reviewed and a definite indentation of the greater curvature of the stomach was already present.

Loss of weight was recorded in 54 of 65 cases in which a history was obtainable. Carcinoma of the pancreas should be considered when there is a rapid loss of weight not due to diabetes, hyperthyroidism, tuberculosis, anorexia nervosa, sprue, or gastrointestinal malignancy. A loss of weight occurs in about 90 per cent of cases. The loss is usually rapid and averages about 25 pounds.

Anorexia occurred in most of the patients from whom a history was obtained. *Nausea* and *vomiting* developed in 30 patients. *Constipation* is much more frequent than diarrhea. Thirty of our patients had constipation and seven diarrhea.

Icterus was present in only 37 of our 75 cases. This is due to the fact that in 38 of the cases the carcinoma was in the body, tail or aberrant pancreatic tissue. Jaundice was present in 31 of the 37 cases of carcinoma of the head, indicating that the common duct is not always obstructed in cancer of the head of the pancreas. Jaundice was present in six cases of carcinoma of the body,

tail or of both, due to pressure by metastases. Two carcinomas developed in aberrant pancreatic tissue.

Fever occurred in ten cases, the temperature varying between 100 and 104°F. A *leukocytosis* above 12,000 was found in one-half of the cases in which blood counts were made, usually in those with metastases.

Ascites was present in 29 of the 75 cases, and was found in 30 cases at necropsy. The presence of ascites may lead to a mistaken diagnosis of cirrhosis of the liver. Cytologic examination of the fluid should always be made for the presence of tumor cells. The fluid may be serous or hemorrhagic. The ascites is usually due to peritoneal metastases, but may also result from involvement of the portal vein or vena cava. Levy and Lichtman² in a report of 19 cases of carcinoma of the body and tail of the pancreas found ascites in 6, with hemorrhagic fluid in 4 of these cases. Grauer⁴ reported 34 autopsied cases and found ascites in 8.

Hepatic enlargement was reported in 35 of the 75 cases, although metastases in the liver were found at necropsy in 53 cases. The metastases are often small and multiple and in most cases do not protrude above the capsule.

A *palpable tumor mass* was recorded in 37 of the cases, or about 50 per cent. Because of the location of the pancreas it is often difficult to feel a mass. Careful palpation under fluoroscopic control has enabled us to find the tumor in some cases. A barium meal or barium enema may reveal a filling defect in the stomach wall, duodenal loop, or transverse colon and thus aid in the palpation of the tumor.

A palpable gallbladder was reported in 20 cases. This finding is a valuable aid in diagnosis, especially in the presence of jaundice. It is of even greater value to the surgeon. At operation the gallbladder is found to be enlarged in over 80 per cent of cases of carcinoma of the head of the pancreas.

Edema of the lower extremities was an early finding in eight cases. This edema could not be explained on a cardiac or renal basis. In one patient it preceded the development of abdominal symptoms or findings for a period of six months, and was accompanied by a low blood protein content of 5 to 5.5 per cent. This patient later developed a loss of weight and ascites, and tumor cells were found in the hemorrhagic ascitic fluid. The edema is most likely caused by pressure of tumor masses or thromboses of abdominal veins, a frequent finding at necropsy.

X-ray findings aid in the diagnosis of pancreatic malignancy in about one-half of the cases. Gastric and prepyloric defects, duodenal distortion or defect, displacement of the transverse colon downward, obstruction of the pyloric region or duodenum, or filling defects simulating primary tumor of the stomach, duodenum, or colon may occur. Ulceration with hemorrhage may lead to an erroneous diagnosis of carcinoma of the stomach or bowel. Engel and Lysholm⁶

have suggested distention of the stomach with an effervescent powder to demonstrate a perigastric or retrogastric shadow.

In carcinoma of the head of the pancreas there is often a widening of the C-shaped curve of the duodenum. There may be a narrowing of the lumen due to compression, or even obstruction. The tumor may invade the wall of the duodenum with ulceration and hemorrhage. Sometimes the pyloric region of the stomach is involved leading to a diagnosis of gastric cancer, especially when there is no icterus.

There may be an indentation on the greater curvature or posterior wall of the stomach in carcinoma of the body or tail of the pancreas. The stomach may be displaced upward or forward by the tumor mass. The transverse colon may be displaced downward or invaded. Metastases from the primary tumor may produce similar changes.

Metastases in other parts of the body are not uncommon, as we shall see later. These may produce the first symptoms in the chest, skeletal system, brain or elsewhere.

An x-ray study was made in 46 of our 75 cases. Abnormalities such as we have described were found in 22 cases.

Laboratory Findings.—The icteric index in cases with obstructive jaundice is usually high, with an average around 100. The stools become alcholic or clay-colored. They may contain blood when the carcinoma has invaded the stomach, duodenum, or colon with ulceration.

In obstructive or surgical jaundice the urobilinogen in the urine is reduced or absent. The serum alkaline phosphatase is usually elevated above 15 Bodansky units. The serum total cholesterol may be increased above 300 mg. per cent.

Gastric analysis reveals an anacidity in about 40 per cent of cases of carcinoma of the pancreas. In this series there was an anacidity in 11 of 24 patients examined. In nine the gastric contents gave a positive reaction for blood, and in these the necropsy later revealed ulceration of the stomach or duodenum by the tumor.

Sugar tolerance.—Hyperglycemia is a valuable finding in suspected carcinoma of the pancreas. It is present in 25 to 50 per cent of cases. True diabetes may develop with extensive destruction of the islet tissue. It occurs in about 10 per cent of the cases. The finding of glycosuria should be followed by blood sugar determinations.

Blood amylase and lipase may be increased and furnish a diagnostic aid. However, this is found in only about 20 per cent of cases of carcinoma of the pancreas. Levy and Lichtman² reported an increase of lipase in one of five cases. Blood cholesterol is usually normal. The absence of duodenal ferments is a useful diagnostic finding, but rarely occurs unless the tumor involves the head of the pancreas.

Leukocytosis is frequently found in those cases with cholangitis or cholecystitis, and also with metastases. Anemia is moderate or absent in most cases. When marked, it usually results from secondary ulcerations in the gastrointestinal tract with hemorrhage.

NECROPSY FINDINGS

We have already called attention to the fact that in this series carcinoma of the body and tail of the pancreas was as frequent as that of the head. The following table (Table 2) gives the location of the primary tumor in the 75 cases.

It is interesting to note the location of the primary tumor in the 37 cases with jaundice. Whereas carcinoma of the head of the pancreas was found in 37 cases, jaundice was present in only 31 of these. On the other hand, 6 cases

TABLE 2
Location of Carcinoma of Pancreas

Head.....	37
Tail.....	16
Body.....	12
Body and tail.....	8
Aberrant pancreatic tissue.....	2

TABLE 3
Location of Primary Carcinoma in 37 Cases with Jaundice

Head.....	31
Tail.....	3 (peripancreatic, liver and peribiliary metastases)
Body.....	2 (liver, peritoneal, gallbladder metastases)
Body and tail.....	1 (peribiliary metastases)

of carcinoma of the body and tail developed jaundice due to metastases (Table 3).

Types of Carcinoma.—The following table (Table 4) gives the histologic types reported in 70 of the 75 cases.

The duodenum was infiltrated, with perforation, in three cases. The first portion was involved in 2 cases, second portion in 3 cases, and third portion in 2 cases. The jejunum was infiltrated in 2 cases. The transverse colon was involved in 8 cases, with stenosis in 3 and perforation in 1 case. The rectum was invaded in 2 cases, also the esophagus in 2 cases.

The stomach was involved in 10 cases, with ulceration and hemorrhage in 3 cases. Hemorrhage into the gastrointestinal tract was found in ten cases post-mortem.

The spleen was invaded in 11 cases, usually those of carcinoma of the tail of the pancreas.

Venous thrombosis was a frequent finding. The splenic vein was thrombosed or occluded by tumor tissue in 6 cases. The splenic artery was involved in

TABLE 4
Histologic Types of Carcinoma of Pancreas

Adeno-carcinoma.....	53
Squamous cell.....	3
Cylindrical cell.....	1
Medullary.....	2
Colloid adenocarcinoma.....	2
Spindle cell.....	1
Anaplastic.....	1
Alveolar.....	2
Scirrhus.....	2
Carcinoma simplex.....	2
Undifferentiated.....	1

TABLE 5
Metastases in 75 Cases of Carcinoma of the Pancreas

Liver.....	53	Bones.....	4
Abdominal Lymph Nodes.....	42	Ovaries.....	3
Lungs.....	16	Duodenum, perforation.....	3
Peritoneum.....	16	Esophagus.....	3
Adrenals.....	12	Gastrohepatic ligament.....	2
Mesentery.....	11	Brain and spinal cord.....	2
Spleen.....	11	Abdominal wall.....	2
Stomach.....	10	Hepatoduodenal ligament.....	1
Pleura.....	9	Gastrocolic ligament.....	1
Large intestine.....	9	Umbilicus.....	1
Omentum.....	8	Testis.....	1
Gallbladder.....	6	Thyroid.....	1
Heart and pericardium.....	6	Urinary bladder.....	1
Small intestine.....	5	Uterus.....	1
Diaphragm.....	4	Mediastinum.....	1
Kidneys.....	4	Retroperitoneal fat.....	1

TABLE 6
Lymph Node Metastases

Peri-pancreatic.....	28	Peri-tracheal.....	3
Peri-aortic.....	18	Posterior mediastinal.....	2
Peri-biliary.....	13	Peri-iliac.....	2
Peri-gastric.....	7	Peri-ureteral.....	1
Mesenteric.....	5	Inguinal.....	1
Hilus of lung.....	4	Cervical.....	1
		Peri-rectal.....	1

four cases. The portal vein was involved in four cases. The hepatic artery was thrombosed in two cases and the inferior vena cava in three cases.

There was a right-sided hydronephrosis in three cases due to compression of the right ureter by metastases.

Metastases occurred most frequently in the liver, abdominal lymph nodes, lungs, peritoneum, adrenals, mesentery, stomach, pleura, intestines and omen-

TABLE 7
Clinical Findings in 75 Cases of Carcinoma of the Pancreas

Pain.....	57 of 65 cases with a history
Abdominal.....	37
Epigastric.....	18
Lumbar.....	15
Abdominal and lumbar.....	14
Right upper quadrant.....	7
Left upper quadrant.....	5
Thoracic.....	4
Skeletal.....	4
Right kidney.....	3
Loss of weight (10+ pounds).....	54 of 65 cases
Palpable tumor.....	37
Jaundice.....	37
Enlarged liver.....	35
Constipation.....	30
Ascites.....	29
Vomiting.....	25
Palpable gallbladder.....	20
Nausea.....	14
Fever (100°F. +).....	10
Diarrhea.....	7

TABLE 8
Laboratory Findings in Carcinoma of the Pancreas

Hyper-bilirubinemia.....	50%
Reduced or absent urobilinogen in urine.....	50%
Abnormal x-ray findings.....	40%
Anacidity.....	40%
Reduced sugar tolerance.....	25%
Increased blood lipase.....	20%
Hyperglycemia.....	15%
Blood in feces.....	10%
Fatty stools.....	10%

tum. They were found in the bones in four cases and in the brain and spinal cord in 2 cases (Tables 5 and 6).

SUMMARY

The early diagnosis of carcinoma of the pancreas is difficult, largely because of the frequency of its occurrence in the body and tail of the pancreas. In this series of 75 cases, 36 originated in the body and tail and two in aberrant pan-

creatic tissue. Thirty-seven cases developed in the head of the pancreas, but in six of these there was no jaundice.

Pain and a rapid loss of weight are present in 80 to 90 per cent of all cases. A painless progressive jaundice therefore occurs in a small per cent of patients. Pain was present in 57 of the 65 cases in which a history was obtainable. It was abdominal in 37, epigastric in 18, lumbar in 15, abdominal and lumbar in 14 and thoracic in 4.

The chief clinical findings were a palpable liver (65 per cent); palpable tumor mass (45 per cent); jaundice (45 per cent); palpable gallbladder (33 per cent) and ascites (25 per cent).

A careful x-ray study yields valuable aid in 40 per cent of cases. The blood lipase is increased in 20 per cent and sugar tolerance is reduced in 25 per cent of cases.

Necropsy findings revealed frequent metastases in the liver (70 per cent), abdominal lymph nodes (56 per cent), lungs (20 per cent), peritoneum (20 per cent), adrenals (16 per cent), and in other organs.

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RESPONSE OF SERUM AMYLASE AND LIPASE TO PANCREATIC STIMULATION AS A TEST OF PANCREATIC FUNCTION

THE MECHOLYL-SECRETIN AND THE MORPHINE-SECRETIN TESTS*

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INTRODUCTION

An adequate, simple test of pancreatic function thus far has not been made available. Determinations of serum enzyme values when done promptly during the acute attacks in the earlier stages of chronic relapsing pancreatitis may be extremely helpful in establishing the diagnosis and are reasonably adequate when properly performed. When the disease has progressed to include the manifestation of steatorrhea, diabetes mellitus and pancreatic calcification the diagnosis is evident. In the stages between these two extremes, however, there is that large group of such patients who of necessity remain as real diagnostic problems because of the lack of an adequate test of pancreatic function. The secretin test utilizing duodenal intubation which has been developed and employed with fair success at a few research centers is cumbersome, time-consuming and often difficult to interpret.

Several investigators have produced in animals an elevated value of serum amylase following the injection of pilocarpine^{1, 2, 3} and of acetyl-beta-methylcholine chloride (mecholyll chloride).⁴ Some of these have demonstrated the pancreatic origin of the serum enzyme in such experiments employing stimulation by means of mecholyll chloride combined with eserine⁵ and pilocarpine with acetylcholine.⁶ In a comparative study of different pancreatic stimulants in humans Comfort and Osterberg⁷ observed that the administration of secretin plus mecholyll chloride effected the greatest secretion into the duodenum, but values of serum enzymes were not determined. Popper et al.^{8, 9} have studied in dogs the response of serum amylase and lipase to the administration of secretin and mecholyll chloride. They and Friedman and Thompson⁵ suggested that such a procedure might be of value as a clinical test of pancreatic function in humans thus avoiding the need for duodenal intubation. This hope has been reiterated in standard textbooks.^{10, 11} Part of the present study was undertaken to evaluate such a test in the human subject. Lagerlöf¹² in 1945 administered secretin intravenously to stimulate pancreatic secretion and at the same time

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injected morphine sulfate subcutaneously theoretically to produce spasm of the sphincter of Oddi thus causing obstruction to the flow of the external pancreatic secretion. He reported that this procedure "often" caused an elevation of serum amylase at which time many subjects experienced pain characteristic of biliary dyskinesia with clinical signs of a mild pancreatitis. This reaction occurred chiefly among individuals who had undergone cholecystectomy, but also in patients with a normally functioning gallbladder. When the test was repeated, eleven of these subjects exhibiting a great elevation of amylase showed an elevated value of serum lipase as well. The present study was undertaken to evaluate as a test of pancreatic function the response of pancreatic stimulation by various means as reflected in alterations in the values of the serum enzymes.

METHODS

Serum amylase was determined by the Somogyi method.¹³ Incubation times were determined to the nearest minute. The range of error in duplicate and triplicate determinations of the same specimen of normal serum was from 0 to 36% with a mean error of 6%. The mean control amylase value based on 36 normal subjects was 146.4 units with a standard deviation of 55.7. Using three times the standard deviation as a criterion, the upper limit of normal for this group would be 313.5 Somogyi units.

Serum lipase was determined by the Crandall and Cherry¹⁴ method as modified by Maclay.¹⁵ Titrations were done with 0.1 N NaOH to the nearest 0.1 cc. The range of error on duplicate and triplicate determinations on the same specimen of normal serum was from 0 to 50% with a mean error of 14%. The mean control lipase value based on 37 normal subjects was 0.27 cc with a standard deviation of 0.16. Using three times the standard deviation as a criterion, the upper limit of normal for this group would be 0.75 cc of 0.1 N NaOH.

A positive response was considered a significant elevation of serum amylase or lipase after administration of the various pancreatic stimulants. To determine the lower limit of a positive response, the enzyme values of subjects without a positive response were utilized. For serum amylase the mean increase was 8.2 ± 13.3 ($N = 24$). The corresponding values for serum lipase were 0.05 ± 0.12 ($N = 24$). Therefore, using three times the standard deviation as the level of significance, any increase compared to the control value of over 48 units of serum amylase or of 0.4 cc of 0.1 N NaOH was considered a positive response. This is justified by the clear cut division with few exceptions of the 62 subjects into two such distinct groups; i.e., those with no apparent change of enzyme values compared to the control values and those with a definite marked change.

PROCEDURES AND RESULTS

Part A. Mecholyl and Secretin in Normal Subjects

To each of eight normal fasting males were administered 20 mg. of mecholyl chloride subcutaneously followed in five minutes by 160 clinical units (twice the standard dose) of secretin (Astra) intravenously. Control values of serum amylase and lipase were determined prior to medication and determinations were made at intervals of 30, 60, 90, and 120 minutes after the drugs were given.

Compared to the control values there was no significant change in the values of serum lipase, although two subjects had a questionably positive response in serum amylase. No untoward symptoms were produced. The usual effects of mecholyl chloride were noted.

Part B. Secretin (Lilly) Alone in Normal Subjects

Inasmuch as this secretin (Lilly) is believed to be more potent than secretin heretofore available, it was important to determine whether this material alone might alter the serum enzymes. For this purpose, 15 mg. were administered intravenously to each of nine normal individuals. Control values of serum amylase and lipase were compared with values determined at two and four hours after the medication. In a few subjects determinations were also made at one hour after the secretin was given.

Of the nine subjects given secretin alone, only one subject had a significant elevation of both serum amylase and lipase and one subject had a slight elevation only of serum amylase. Three subjects previously had shown an elevation of serum enzymes over the control values with the combination of morphine sulfate and secretin (To be described).

Part C. Mecholyl and Secretin (Lilly) in Normal Subjects

Each of 24 males who presented no gastrointestinal complaints were given 20 mg. of mecholyl chloride subcutaneously followed in five minutes by 15 mg. of secretin intravenously. Serum amylase and lipase determinations were made at one and two hour intervals after the drugs were administered.

Seventeen of the 24 subjects (70%) gave a positive response as indicated by a significant elevation above the control value of either the serum amylase or lipase following administration of the medications. In 15 (62%) the amylase determination alone was elevated and in 17 (70%) the lipase determinations were elevated over the control values. In the subjects with a positive response there was a wide range of values of serum amylase and lipase. The mean values and standard deviations are shown in Table 1. There was no statistically significant difference between the values at one hour and two hours. There appeared

to be good correlation between the increase in serum amylase and the increase in serum lipase. This was particularly true with the determinations made after one hour ($r = 0.90$, $N = 15$).

Part D. Morphine Sulfate and Secrelin (Lilly) in Normal Subjects

Thirty males without gastrointestinal complaints were subjects. The first 11 subjects were given 10 mg. of morphine sulfate subcutaneously and 30 minutes later, 15 mg. of secretin were administered intravenously. In the remaining 19 subjects the secretin was given five minutes after the same dose of morphine sulfate. A determination of values of serum amylase and lipase was made prior to medication to serve as a control and following the injection of secretin at

TABLE 1

Means and standard deviations of 15 subjects with a positive serum amylase response and 17 subjects with a positive serum lipase response in 24 normal subjects given the mechatyl-secretin test

	AMYLASE			LIPASE		
	Control	1 Hr.	2 Hr.	Control	1 Hr.	2 Hr.
Mean.....	156.9	452.7	480.2	0.29	1.59	1.28
Standard Deviation.....	59.5	213.5	245.3	0.16	0.75	0.64

TABLE 2

Means and standard deviations of 21 subjects with a positive serum amylase response and 20 subjects with a positive serum lipase response in 30 normal subjects given the morphine-secretin test

	AMYLASE			LIPASE		
	Control	2 Hr.	4 Hr.	Control	2 Hr.	4 Hr.
Mean.....	138.9	590.4	598.7	0.24	2.25	1.60
Standard Deviation.....	47.9	394.6	414.3	0.16	1.12	0.92

intervals of two and four hours. In a few instances the determinations were made at more frequent intervals.

In this group of 30 subjects a positive response was found in 21 (70%) for serum amylase and 20 (66%) for serum lipase. Again in those patients with a positive response there was a wide range of values of serum amylase and lipase. The mean and standard deviations are shown in Table 2. No significant difference was noted between the groups receiving the secretin at five minutes and at 30 minutes after the morphine sulfate. In one subject the test was repeated approximately a week later with an increased dose of 15 mg. of morphine sulfate and again there was no elevation of the serum enzymes.

No clinical symptoms of pancreatitis were produced. There were no significant reactions to the medications. A slight facial flush was noted in approxi-

mately 50% of the subjects. In the few instances in which the serum amylase and lipase were determined 24 hours after the test, the enzyme values were normal.

One subject who did not have a positive response to the mecholyl-secretin test did give a markedly positive response to the morphine-secretin test nine days later. The control serum amylase and lipase values were 200 Somogyi units and 0.1 cc. of 0.1 N NaOH respectively, the one-hour values 666 units and 2.3 cc. respectively, and the two-hour values 800 units and 2.3 cc. respectively.

Part E. Morphine and Secretin (Lilly) in Subjects with Pancreatic Disease

Nine subjects with far advanced disease of the pancreas received the morphine-secretin test as described under Part D with a five minute interval between the administration of the morphine and the secretin:

1. Male aged 62 years with a 10 year history of recurrent bouts of severe epigastric pain who had diabetes mellitus and pancreatic calculi by roentgenographic examination.

2. Male aged 35 years with a 4 year history of recurrent bouts of severe epigastric pain and who had just developed diabetes mellitus. At operation the gallbladder was normal and the pancreas diffusely hard and fibrotic.

3. Male aged 53 years who had far advanced hemochromatosis and diabetes mellitus. Liver biopsy showed large deposits of iron.

4. Male aged 59 years who had a history of two attacks of severe epigastric pain requiring opiates for relief. Cholecystogram was normal and roentgenograms of the abdomen revealed large numbers of pancreatic calculi.

5. Male aged 59 years who had diabetes mellitus and on surgical exploration was found to have a diffusely hard fibrotic pancreas.

6. Male aged 55 years who complained of epigastric discomfort for many years. Roentgenogram of the abdomen revealed pancreatic calculi.

7. Female aged 43 years who had recurrent bouts of severe epigastric pain, diabetes mellitus and tuberculosis. Roentgenographic examination revealed pancreatic calculi. Surgical exploration disclosed a normal gallbladder and a hard fibrotic pancreas.

8. Male aged 36 years with a large number of pancreatic calculi by roentgenographic examination.

9. Male aged 36 years with diabetes mellitus and pancreatic calculi by roentgenographic examination.

Subject 2 experienced some epigastric pain associated with mild nausea which lasted approximately one hour. This distress was similar to, but not nearly so severe, as that related to his disease. Subject 4 experienced some nausea, vomiting and weakness, unassociated with pain which occurred about five hours following the test.

In no instance was there a significant elevation of the values of serum amylase or lipase as compared to the control values as is shown in Table 3. Seventy per cent of 30 normal subjects gave a positive response to this morphine-secretin test and since there was no positive response among the nine subjects with advanced disease of the pancreas, it is estimated that the probability of occurrence by chance of a difference of this magnitude is 0.0002.

TABLE 3

Morphine-secretin test in nine subjects with far advanced disease of the pancreas

SUBJECT	SERUM ENZYME	CONTROL	1 HR.	2 HR.	4 HR.
1	Amylase	<80	<80	<80	<80
	Lipase	<0.1	<0.1	<0.1	<0.1
2	Amylase	<80	<80		<80
	Lipase	0.2	0.1	0.2	0.2
3	Amylase	<80		<80	<80
	Lipase	0.4		0.4	0.3
4	Amylase	115		123	123
	Lipase	0.5		0.5	0.5
5	Amylase	84		106	100
	Lipase	0.2		0.2	0.2
6	Amylase	200		200	200
	Lipase	0.1		0.2	0.2
7	Amylase	106		106	115
	Lipase	<0.1		<0.1	<0.1
8	Amylase	355		355	355
	Lipase	0.7		0.8	0.6
9	Amylase	145		160	160
	Lipase	0.2		0.2	0.2

DISCUSSION

There is a great need for an adequate, reasonably simple diagnostic procedure for studying pancreatic function. Thus far there has not been made available any means by which mild or early pancreatic dysfunction may be detected. When done promptly in the acute attack during the early stages of chronic relapsing pancreatitis, the determination of serum amylase and lipase may be helpful.

With the hope of formulating a relatively simple test of pancreatic function, the values of the serum amylase and lipase have been studied following pancreatic stimulation by a variety of means. It was hoped that a standard response might occur in normal subjects from which an abnormal response, in the event of pancreatic dysfunction, could be distinguished.

Intravenously administered secretin (Astra) in large dosage combined with mecholyl administered subcutaneously in 8 subjects and secretin (Lilly) alone administered intravenously in 9 subjects did not produce an elevation of

serum amylase and lipase except in one instance with the latter material. When mecholyl was given subcutaneously combined with a large dose of secretin (Lilly) administered intravenously, there resulted a significant elevation of either serum amylase or lipase in 70% of 24 normal subjects. The combination of morphine sulfate administered subcutaneously with secretin (Lilly) intravenously produced a significant elevation of serum amylase or lipase in 70% of 30 subjects.

It is interesting that there is no difference in the percentage of positive response to the morphine-secretin test and to the mecholyl-secretin test. The mechanism of a positive response with mecholyl is not definitely known, but with the morphine a spasm of the sphincter of Oddi and resultant back pressure into the pancreatic duct system is postulated. It may well be at least in the morphine-secretin test that the response which limits the test depends upon the anatomical variations of the pancreatic duct. Probably no other region of the body presents more variations. In approximately 76% of one series¹⁶ the main pancreatic duct and the common bile duct were found to have a common orifice in the duodenum. Whether or not this group represents those individuals who may give a positive response to the morphine-secretin test because of the anatomic feature cannot be stated.

Nine subjects with far-advanced pancreatic disease were given the morphine-secretin test and in no instance was there an elevation of serum enzymes. The difference in response between the normal group and the group with pancreatitis is statistically highly significant. This may indicate a lack of functioning acinar pancreatic tissue in the subjects with pancreatitis.

A positive response, i.e., significant elevation of serum amylase or lipase after the mecholyl-secretin or morphine-secretin stimulation in 70% of the subjects is not sufficiently great as such for a test of pancreatic function. One subject who did not respond to the mecholyl-secretin test did respond to the morphine-secretin test. A positive response after such stimulation at least is indicative of functioning pancreatic tissue and thus might be of value in differentiating pancreatogenous steatorrhea from that of sprue.

SUMMARY AND CONCLUSIONS

1. A study has been made of the response as reflected in alterations in the values of serum amylase and lipase to pancreatic stimulation by various means.
2. The administration of a large dose of secretin (Astra) intravenously and mecholyl chloride subcutaneously to 8 normal subjects failed to elevate significantly the values of these enzymes.
3. A recently available secretin preparation (Lilly) administered intravenously to nine normal subjects produced a significant elevation of serum amylase and lipase in one instance.

4. The administration of mecholyl subcutaneously and secretin (Lilly) intravenously to 24 normal subjects resulted in a significant elevation of values of either serum amylase or lipase as compared to control values in 70%. The percentage of positive response to this mecholyl-secretin test is not sufficiently great to merit clinical utilization as a means of studying pancreatic function.

5. The administration of morphine sulfate subcutaneously and secretin (Lilly) intravenously to 30 normal subjects produced a distinct increase in the values of serum amylase or lipase in 70% of these. The percentage of positive response to this morphine-secretin test is not sufficiently large to merit clinical utilization as a means of studying pancreatic function. The morphine-secretin test was given to nine patients with far advanced disease of the pancreas and in no instance was there a significant elevation of pancreatic enzymes.

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EXTERNAL PANCREATIC SECRETION AS MEASURED BY THE SECRETIN TEST IN PATIENTS WITH IDIOPATHIC STEATORRHEA (NONTROPICAL SPRUE)

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It is generally believed that external pancreatic secretion in patients with idiopathic steatorrhea (nontropical sprue) is normal but recorded data apparently are few in number. Comfort, Parker and Osterberg¹ found pancreatic enzymes in normal concentrations in nonstimulated fasting duodenal contents in 6 cases. Childs and Dick² and Snell³ each reported similar findings in a single case. Lagerlöf⁴ reported normal external pancreatic function as measured by the secretin test in 2 cases. Diamond, Siegel and Meyerson,⁵ studying 14 cases of steatorrhea which clinically resembled sprue, reported normal external pancreatic function as measured by the secretin test in 4 cases but in the remaining 10 there was evidence of pancreatic disturbance. This was characterized particularly by marked deficiencies in lipase, which in most instances was temporary and reversible, the value returning to normal coincident with the clinical improvement of the patient. To these data on external pancreatic function in nontropical sprue we wish to add those obtained from a study of 13 cases, employing the secretin test.

SUBJECTS STUDIED

The data on the 20 normal subjects used as controls have been previously published.⁶ The diagnosis of idiopathic steatorrhea (nontropical sprue) has been based upon the characteristic history of a chronic fatty diarrhea, weight loss and sore mouth together with one or more of the following: macrocytic anemia, flat glucose tolerance curve, the so-called deficiency pattern of the small bowel observed by the roentgenologist, hypoproteinemia with or without peripheral edema, hypocalcemia with or without tetany and osteoporosis, and hypoprote thrombinemia with or without a clinically manifested bleeding tendency. In all cases, other causes of steatorrhea have been excluded. The findings in each case are presented in table 1. In all 13 cases the diagnosis appears to be clear-cut.

PROCEDURES AND LABORATORY METHODS

The procedures and laboratory methods used have been previously described.⁶ Purified secretin (pancreatost, manufactured by Astra in Sweden) was used.

RESULTS

Analysis of the Duodenal Contents Before Stimulation With Secretin.—Data from analyses of duodenal contents collected during the first and second ten-minute periods before the administration of secretin are not presented in de-

TABLE 1
Data on 13 Patients With Idiopathic Steatorrhea*

CASE	AGE AND SEX	STEA-TORRHEA	FLAT SUGAR CURVE	ANEMIA		ROENT-GENO-GRAM†	SERUM PRO-TEINS, GM. PER 100 CC.	EDEMA	SERUM CAL-CIUM, MG. PER 100 CC.	TETANY	PRO-THROM-BIN TIME, SECONDS‡
				Macro-cytic	Micro-cytic						
1	40F	+	+	+		+	4.4	+	7.1		160
2	27M	+	+	+		+	3.9	+	8.9		51
3	52F	+	+	+		+	4.5	+	4.5	+	39
4	43F	+	+		+	+	5.9		5.1	+	54
5	40F	+	+	+		+	4.1	+	8.5		25
6	36F	+	+	+		+	6.3		8.8		
7	63F	+		+		+	7.0		5.2	+	
8	30M	+	+	—	—	+	4.2	+	7.5		26
9	46M	+	+	+		+	7.4	+	7.0		26
10	26F	+	+	+		+	4.6	+	6.6		30
11	53M	+	+		+	+	5.8	+	9.3		19
12	24M	+	+	—	—	+	3.8	+	8.2		21
13	37F	+		—	—	+	6.4		9.3		

* A + unless otherwise stated means condition is present; a — means that it is absent or normal conditions obtain; blanks mean no data.

† A + indicates a characteristic "deficiency pattern" in the small bowel.

‡ Normal value is 17 to 19 seconds (modified Quick method).

tail. The results may be summarized by saying that values for total volume, concentration and total bicarbonate, and for total enzymes fell within normal limits.*

Analysis of the Duodenal Contents After Stimulation With Secretin. (table 2). Volume.—The mean total volume for the forty minutes after stimulation was 139.2 cc. This value was more than the corresponding value for normal persons (122.5 cc.), but the difference is not statistically significant. In each of the 13 cases, the value for volume was more than the presumptive lower limit of normal which was calculated by subtracting two times the standard deviation from the normal mean.

* The mean for normal persons \pm two times the standard deviation has been considered normal limits.

Bicarbonate.—The mean concentration of bicarbonate for the forty-minute period after stimulation was 0.090 millimols per cubic centimeter, as compared with 0.105 millimols per cubic centimeter for normals. The difference between the means (0.015 millimols) is not statistically significant. In cases 10 and 13 the

TABLE 2

Values for Average Concentration of Bicarbonate and for Total Volume, Bicarbonate, Amylase, Trypsin and Lipase in 13 Patients With Idiopathic Steatorrhea (Sprue) for the Forty-minute Period Following Stimulation with Secretin

CASE	VOLUME	BICARBONATE		AMYLASE, GM. OF MALTOSE	TRYPSIN, CC. OF TENTH- NORMAL POTASSIUM HYDROXIDE	LIPASE, CC. OF TWENTIETH- NORMAL SODIUM HYDROXIDE
		Millimols per cubic centimeter	Millimols total			
	cc.					
1	139	0.100	15.5	284	158	31,480
2	211	0.087	17.3	277	123	36,788
3	115	0.110	12.6	117	68	928
4	84	0.113	9.6	44	57	6,741
5	169	0.090	14.5	157	176	17,840
6	175	0.083	14.8	60	126	10,498
7	82	0.108	8.6	19	75	2,913
8	104	0.080	9.1	131	118	
9	119	0.093	11.3	57	112	
10	186	0.073	13.0	51	246	
11	129	0.085	9.6	159	192	12,532
12	163	0.080	12.8	37	133	11,402
13	133	0.073	10.6	72	169	7,866
Mean*.....	139.2±10.9	0.090±0.005	12.3±0.8	112.7±24.2	134.9±14.8	13,898±3,229
Standard deviation.....	39.5	0.016	2.7	87.3	53.4	10,244
Normal mean.....	122.5±6.4	0.105±0.004	14.8±1.0	91.0±9.6	117.7±11.4	10,519±1,335
Normal standard deviation.....	28.7	0.014	3.5	43.0	49.4	5,820
Difference from normal†.....	16.7±11.9	0.015±0.005	2.5±0.9	21.7±22.9	17.2±18.2	3,480±3,152

* The figure following the \pm is the standard error of the mean.

† Difference between the normal mean and the mean of this group.

concentrations of bicarbonate were slightly less than the presumptive lower limit of normal, but in each of these 2 cases the values for volume and total bicarbonate were well within normal limits.

The mean value for total bicarbonate for the forty-minute period after stimulation was 12.3 millimols. This value was less than the corresponding

value for normal persons (14.8 millimols) but the difference is not statistically significant. In each of the 13 cases the value fell well within normal limits.

Enzymes.—The mean values for total enzymes were slightly higher than corresponding values in normal subjects, but these differences were not statistically significant. The values for total enzymes in each of the 13 cases fell within or above normal limits.

SUMMARY AND DISCUSSION

In the 13 cases of this series the values for volume, concentration of bicarbonate, total amylase, trypsin and lipase in the forty-minute sample after stimulation with secretin, were within or above the limits of normal. (Two values for concentration of bicarbonate were borderline.) Such values are interpreted to mean that external pancreatic function was normal.

Normalcy of function, as measured by the secretin test, probably means that pancreatic dysfunction did not play a role in the steatorrhea in these 13 cases. It is true that the secretin test is not sensitive enough to measure minor degrees of external pancreatic dysfunction but it has measured deficiencies of the external pancreatic function in cases in which the destruction of the pancreas has not been sufficient to produce steatorrhea or azotorrhea. Among others, Lagerlöf, and Dornberger, Comfort, Wollaeger and Power have reported such cases. More important, the test has demonstrated a marked deficiency in external pancreatic function in each reported case of pancreatitis or carcinoma of the pancreas in which steatorrhea is known to have been present. Lagerlöf reported 4 cases of pancreatitis and 1 of carcinoma of the pancreas with steatorrhea. In each case the external pancreatic function was markedly subnormal. Dornberger, Comfort, Wollaeger and Power⁶ reported 13 cases of chronic pancreatitis with steatorrhea in which a secretin test was done. In 3 of the 13 cases the steatorrhea was minimal and could be measured only by careful intake-excretion studies. In all 13 cases, even in the 3 in which there was minimal steatorrhea, external pancreatic function as measured by the secretin test was definitely subnormal. In the light of this limited experience, it is not unreasonable to expect a definite deficiency of external pancreatic function, as measured by the secretin test, in cases of idiopathic steatorrhea, if pancreatic deficiency plays a role in producing the steatorrhea.

As previously mentioned, Diamond, Siegel and Meyerson concluded that the secretin test disclosed transitory disturbances of external pancreatic function in 10 of their cases of steatorrhea which clinically resembled sprue. Unfortunately, differences in duration of collection of samples and in chemical methods employed prevent accurate comparison of their data with ours. However, several comments appear pertinent.

First, in 9 of the 10 cases, Diamond, Siegel and Meyerson obtained values

for concentration of bicarbonate well above the lower limit of normal obtained by us in a series of normal persons. In the tenth case the value was borderline. It would appear that the capacity of the pancreas in these cases to secrete bicarbonate was unimpaired.

Second, in only 4 tests performed by Diamond and his associates was the volume of secretion lower than the lower limit of normal accepted by these investigators. In each of the 4 tests the value for concentration of bicarbonate was well within the normal range. At this time we are inclined to believe that a low volume in the presence of normal concentration of bicarbonates indicates not dysfunction, but that the collection of duodenal contents has not been quantitative.

Third, Diamond and his associates speak of a "functional disturbance of the pancreas characterized particularly by marked deficiency in lipase." Since this splendid early work with the secretin test, similar studies have not identified a type of pancreatic deficiency characterized chiefly by deficiency in lipase.

Fourth, evidences of external pancreatic insufficiency, as measured by the secretin test, in known cases of pancreatic disease appear usually to form a distinct pattern. In a recent study of 28 proved cases of chronic relapsing pancreatitis, Dornberger, Comfort, Wollaeger and Power found definite evidence of external pancreatic insufficiency in 23 of the 28. The combination of low values for volume, bicarbonate and enzymes and especially those for volume and bicarbonate characterized the pattern of secretion in external pancreatic insufficiency. The values for volume, concentration of, and total, bicarbonate were more often statistically significant than were those for enzymes. Lagerlöf's type I reaction, with which there has been little experience, appears to be a possible exception. It is not surprising that values for volume and bicarbonate more frequently were of value statistically in establishing a diagnosis of external pancreatic insufficiency than were values for enzymes, because present evidence indicates that secretin primarily is concerned with the stimulation of secretion of water and bicarbonate, not of enzymes. It seems important to point out that in not a single case reported by Diamond, Siegel and Meyerson was pancreatic dysfunction of the type seen in pancreatitis observed.

A transitory disturbance of pancreatic function in sprue might well be expected to occur because of its marked nutritional, metabolic and electrolyte disturbances but it is doubtful that the data so far presented support such a concept.

The failure to demonstrate impairment of external pancreatic function in these 13 cases of idiopathic steatorrhea and the demonstration of impairment in each case of steatorrhea due to pancreatic disease, so far as we have been able to ascertain, suggest that the secretin test may ultimately prove to be a valuable one in the differentiation of steatorrhea due to pancreatitis from that due to idio-

pathic steatorrhea. However, from a practical standpoint, rarely if ever will the secretin test be needed for differential diagnosis between these two types of steatorrhea. This is so because the diagnosis of idiopathic steatorrhea usually can be made on the basis of the characteristic history and the combination of steatorrhea with the several deficiency states found in that disease; the diagnosis of steatorrhea due to pancreatitis may be made on the basis of the history, especially of recurring episodes of pain, the common association of pancreatic calcification and diabetes with steatorrhea of pancreatitis, and the absence of those deficiency states which are so characteristic of idiopathic steatorrhea. Tests needed to demonstrate these several diagnostic features of the two diseases are common laboratory procedures which are less time-consuming and expensive than the secretin test.

CONCLUSIONS

The duodenal contents in 13 cases of idiopathic steatorrhea (nontropical sprue) have been analyzed for volume, bicarbonate and enzyme content before and after stimulation with secretin. Comparison of each of these values with similar values found in normal subjects failed to show changes characteristic of external pancreatic insufficiency. The data obtained indicate that external pancreatic insufficiency does not contribute to the steatorrhea in these cases.

The secretin test apparently may be used to differentiate the steatorrhea of idiopathic steatorrhea from that of pancreatitis but from a practical standpoint this differentiation may be accomplished by clinical data and by less expensive and time-consuming laboratory methods than the secretin test.

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THE CONCURRENCE OF MIGRAINE AND PEPTIC ULCER

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In an attempt to analyze the relationship between migraine and peptic ulcer, we made a careful study of 417 cases of migraine observed in the section of one of us (B. T. H.) at the Mayo Clinic in a period of five years. The following definition of migraine was used as a criterion for selecting these cases. "Migraine is a periodic, recurrent, strongly familial autonomic irritative reactive pattern. It is characterized by the simultaneous occurrence of cephalgia, gastro-intestinal dysfunction, and cortical sensory or motor disturbance or both together with the absence of any impairment of psychic or demonstrable causative pathological lesion."¹ All cases of atypical migraine, mixed headache (migraine and tension headache), histaminic cephalgia and various other types of headache were thereby excluded.

Peptic ulcer was present in 13 (3.1 per cent) of the 417 cases (table 1). The diagnosis of peptic ulcer was confirmed by roentgenologic examination in all of the 13 cases. In 404 of the 417 cases, the history and the results of physical and laboratory examinations did not reveal any evidence of peptic ulcer.

In 11 of the 13 cases, the ulcer was situated in the duodenum (table 1); in the 2 remaining cases, it was situated in the stomach. Seven of the 13 patients were females. In all of the cases in which peptic ulcer developed, the initial attack of migraine occurred before the first symptoms of the ulcer were observed. The period that elapsed between the initial attack of migraine and the first appearance of symptoms of peptic ulcer ranged from three to forty years and averaged about twelve years. There did not appear to be any relationship between the actual attacks of migraine and the occurrence of symptoms attributable to peptic ulcer. In most of the 13 cases in which peptic ulcer occurred, the patients had been taking ergotamine tartrate, and all of these patients at one time or another had taken an antacid and had used an ulcer diet because of the presence of indigestion. No mention of the excessive use of coffee, tobacco or alcohol was made in the history of any of these 13 patients. In 6 of the cases, the patients were of an asthenic type; in the remaining 7 cases, they were of a sthenic type. There was evidence of an anxiety reaction pattern in all of the 13 cases. A diagnosis of constitutional inadequacy could have been made in many of these cases. In fact, all of the 13 patients who had a peptic ulcer also had evidence of a "migrainous personality" which has been defined by Alvarez.²

Most of the patients who had peptic ulcer also had variable degrees of chronic nervous exhaustion, which is significant since Lillehei and Wangenstein³ recently reported that continuous activity and fatigue was a predisposing cause of peptic ulcers in dogs.

TABLE 1
Incidence of Peptic Ulcer in 417 Cases of Migraine

YEAR	CASES OF MIGRAINE	PEPTIC ULCER		TYPE OF PEPTIC ULCER	
		Number	Per cent	Gastric	Duodenal
1943	43	1	2.3		1
1944	43	1	2.3		1
1945	57	1	1.8		1
1946	103	2	1.9		2
1947	171	8	4.7	2	6
Total.....	417	13	3.1	2	11

COMMENT

The incidence of peptic ulcer was 3.1 per cent in the 417 cases of migraine which formed the basis for this study. This is below the reported incidence of peptic ulcer among the general population. In the 13 cases in which a peptic ulcer developed, the initial attack of migraine occurred from three to forty years before the first appearance of symptoms of peptic ulcer. Eusterman and Balfour⁴ stated that between 10 and 12 per cent of all persons suffer from peptic ulcer during their lives.

In the 13 cases in which peptic ulcer occurred, no bodily type predominated and the association of peptic ulcer and migraine could not be explained by the available psychiatric data. There was no relationship between the occurrence of the attacks of migraine and the exacerbation of peptic ulcer.

One of us (B. T. H.)⁵ in 1943 first demonstrated the relationship between acute duodenal ulcer and histaminic cephalgia. The formation of the ulcer in each instance had been secondary to the attacks of histaminic cephalgia. During these attacks of histaminic cephalgia, the values for the gastric acidity rose to an abnormally high level, just as they would if the patient had received approximately 0.35 mg. of histamine base subcutaneously. It was further demonstrated that patients with histaminic cephalgia were hypersensitive to histamine—so much so that 0.01 mg. histamine base had been sufficient in many instances to precipitate a rise in gastric acidity which was comparable to that which occurred in normal persons following the subcutaneous administration of 0.35 mg. of histamine base. Furthermore, treatment of the histaminic cephalgia by means of histamine desensitization (Horton's method)

without other treatment for the duodenal ulcer itself not only eradicated the attacks of histaminic cephalgia but permitted the duodenal ulcer to heal promptly within two or three weeks. Alford and Whitehouse⁶ confirmed these observations regarding the relationship of histaminic cephalgia and duodenal ulcer.

Histaminic cephalgia and migraine represent 2 distinct clinical entities. Histaminic cephalgia is a specific unilateral type of headache which has recently been recognized and fully described. Migraine, on the other hand, has been recognized for centuries. That acid is the important factor in the production of peptic ulcer in man has been postulated by many observers. Studies on experimental animals lend support to this theory.⁷ Allergic gastric and duodenal edema has been produced in experimental animals, which predisposes to histamine-provoked ulcers.⁸

There is hardly a tissue in the body which does not in some way respond to the action of histamine. Of these various tissues, the gastric mucosa is the most sensitive. Hence the rise in gastric acidity can be used as an index for measuring the concentration of histamine in the blood. The abnormal release of histamine from sensitized cells and the role which it may play in the production of peptic ulcer is a thought which will continue to intrigue clinical investigators.

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THE MANAGEMENT OF MASSIVE ESOPHAGEAL HEMORRHAGE WITH TAMPONADE AND THROMBIN*

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The treatment of actively bleeding esophageal varicosities has been essentially supportive due to our inability to control the hemorrhage at its source. Bed rest, morphine and blood replacement have been the recognized therapeutic measures in the past. Except in the presence of a specific deficiency, it is doubtful whether intravenous calcium, thromboplastin, ascorbic acid or vitamin K will actually influence massive bleeding. The esophagoscopy injection of the varix with sodium morrhuate solution has been recommended as an emergency measure,¹ however, poor visualization sometimes makes this a hazardous procedure. Resection of the lower end of the esophagus and ligation of the coronary vein of the stomach has been attempted in a few cases, but major surgical intervention in these exsanguinated patients is a formidable procedure.

Rowntree² and Tocantins³ have reported on the use of intraesophageal tamponade in a total of three cases of actively hemorrhaging esophageal varices. By means of an inflated balloon attached to a double lumen tube, direct pressure was exerted on the bleeding point. For this purpose, a Miller-Abbott tube, which is generally available, may be employed without modification (Fig. 1A). If time is available, simple modifications will improve the function of the tube. Rowntree's adaption consisted of occluding the proximal six holes of the Miller-Abbott tube, and attaching a larger latex bag (Fig. 1B). The modified Rowntree double lumen tube is now available for purchase.

The original Miller-Abbott tube can also be adapted in such a way as to increase the surface contact with the esophageal mucosa, and to permit gavage. By substituting a large latex sheath which communicated with the upper six holes of the double lumen tube, more extensive tamponade is possible. To permit gavage, the metal tip is readjusted so that it will communicate with the lumen containing the lower three holes which had previously been used to inflate the Miller-Abbott balloon (Figs. 1C and 2). Thus, by this rearrangement, the lumen that previously was used for suction, now inflates the latex bag, and the three lower holes and tip are available for feeding.

Once the diagnosis of esophageal hemorrhage secondary to a ruptured varix has been established, the question of the exact location of the bleeding point

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arises. At necropsy the bleeding point is most frequently found at, or just cephalad to, the cardioesophageal ring. According to Tocantins,³ Bixby passed the tube into the stomach, inflated the balloon with air, and then pulled it back against the cardia, securing the external portion of the tube against the nostril to prevent slipping. This procedure will probably successfully tampon most bleeding varicosities. In those cases where the hemorrhage is occurring proximal to the area of contact with the bag, the occlusion of the veins supplying the "bleeder" may well be sufficient to produce hemostasis. Rowntree inflated the

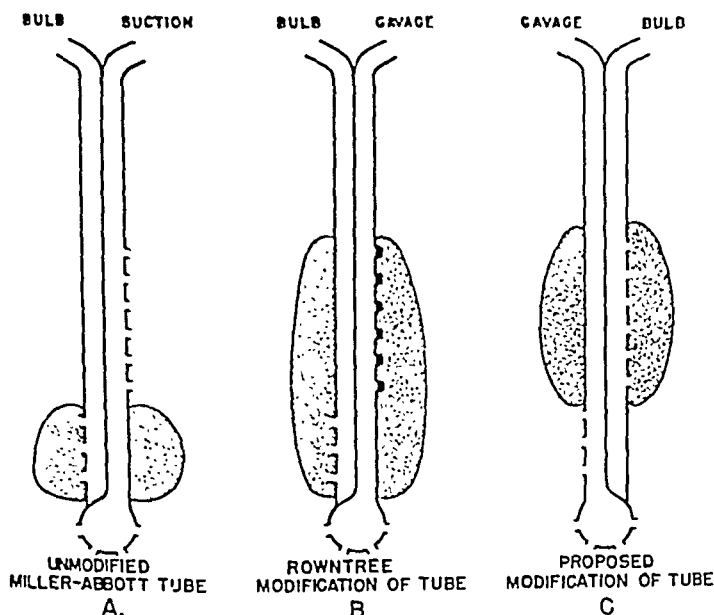


Fig.1

Fig. 1. Diagrammatic sketch of the Miller-Abbott tube and modifications; 1A: Unmodified Miller-Abbott tube; 1B: Rowntree modification with top six holes occluded, balloon attached to lower three holes, and perforations in metal tip for feeding; 1C: The proposed modification of the Miller-Abbott tube with balloon attached to top six holes and lower three holes and metal tip for gavage. The position of the metal tip in the double lumen tube has been reversed.

balloon along the length of the lower esophagus with the distal pole of the bag at the cardia.

We have achieved satisfactory hemostasis by utilizing this principle of cardioesophageal compression in three cases. A Miller-Abbott tube was passed transnasally into the stomach and distended with water containing 20 cc of Diodrast. The amount of water needed for satisfactory compression varies with the type of tube and should be ascertained by a trial filling before passage. The waterfilled bag exerts the most adequate tamponade. The radiopaque fluid permits radiosopic control of the balloon's position. The tube is then

gently pulled up against the cardia until a definite resistance is encountered. To prevent slipping, the external tubing is secured against the upper lip with adhesive. An x-ray film or fluoroscopy should reveal the upper pole of the bag

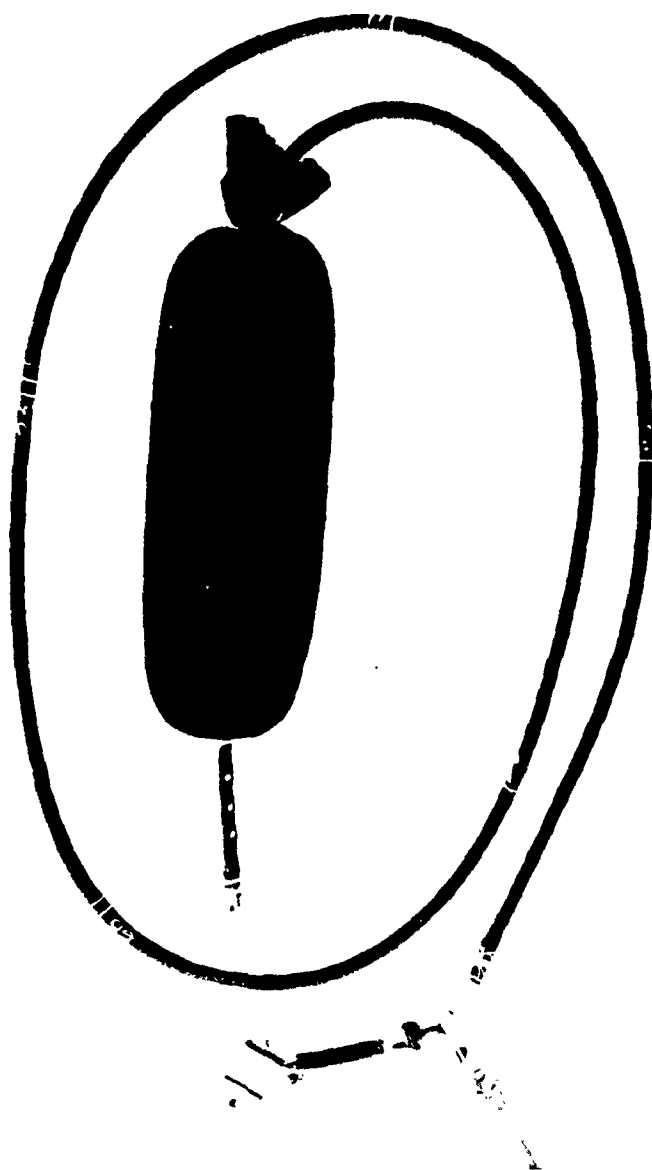


FIG. 2. Our proposed modification of the Miller-Abbott tube to be used for esophageal tamponade and gavage.

at the juncture of cardia and esophagus (Fig. 3). Aspiration of the gastric contents at regular intervals should help detect recurrent hemorrhage.

It is difficult at present to state the length of time that tamponade should be maintained. We feel that between 24 and 72 hours should be sufficient time to

establish satisfactory hemostasis. Although intermittent decompression has been suggested to prevent necrosis of the mucosa, we maintained tamponade for as long as 72 hours without evidence of subsequent pressure necrosis. Because of an experience with recurrence of hemorrhage in one of our cases after



FIG. 3. X-ray of unmodified Miller-Abbott tube inflated with water and diodrast lying in the cardia and pressing against the cardioesophageal junction. Case 2.

removing the tube, we now deflate the balloon at the end of the period of tamponade, and slip the tube into the antrum for a further 12 to 24 hour period. Thus, if repeated suction should reveal renewed bleeding, reestablishment of tamponade can be quickly achieved.

It appeared rational to us to combine the topical application of thrombin with esophageal tamponade. A solution of 10 cc of thrombin in water may be sipped,

or if the patient is comatose, slowly instilled through a Levine tube temporarily placed in the upper esophagus. Theoretically, at least, the tampon should prevent the too rapid passage of the thrombin past the cardia, and the "bleeder" thus might be bathed in a strongly hemostatic solution. During this procedure, the patient should be in Fowler's position to prevent aspiration. During the first 24 hours, the thrombin may be used every four to six hours.

We have treated four cirrhotics exsanguinating from variceal hemorrhages with intraesophageal or cardioesophageal tamponade. Three of these patients also received thrombin solution instillations.

Case 1. P. E. J., a 46 year old unemployed white male who had been drinking one half to one quart of Bourbon whiskey daily for the past 30 years. His food intake had always been poor in quantity and quality. During the past year loss of strength, abdominal and ankle swelling had developed. For the two weeks prior to admission, jaundice, tarry stools and bloody vomitus had been present. The patient was in profound shock when seen on the Reception Service. His blood pressure was 60/30, pulse 110, he was vomiting large quantities of clots and coffee ground material, and involuntarily passing liquid black stools. He appeared emaciated, comatose, and his skin was pale and icteric. His mouth was filled with clotted blood. Dilated superficial veins were seen over the abdomen, and moderate ascites was present. The liver edge was palpable 2.5 cm. below the right costal margin at the midclavicular line. There was a two plus pitting edema of the pretibial area.

The patient appeared terminal, and tamponade of the cardioesophageal ring with a Miller-Abbott tube was established soon after his arrival on the Medical Service. Following this, a solution of 5000 units of topical thrombin in 10 cc. of water was instilled into his esophagus. The patient remained unconscious for two days, during which time a total of 2000 cc. of whole blood, and 2700 cc. of glucose solutions were given by vein. Sixty hours later, the patient was alert, his blood pressure was 137/70, pulse 92, and red blood count four million per cmm. with 79% hemoglobin. Aspirated samples of his gastric contents were grossly free of blood. The tampon was then deflated and removed.

Fourteen hours later, the patient suddenly went into shock, and died before intubation or transfusion could be accomplished. At necropsy, 2000 cc. of clear, yellow fluid was obtained from the peritoneal cavity. The liver was finely granular, and weighed 2360 gm. The cut surface showed marked fibrosis. At the esophago-cardiac juncture, several prominent varicosities were found with distinct areas of ulceration. The stomach was three times normal size and was filled with large quantities of coffee ground material. Microscopic sections confirmed the presence of a Laennec's type of cirrhosis, and submucosal varicosities in the distal esophagus with ulceration and fibrinopurulent reaction.

Case 2. D. T. H., a 61 year old retired naval officer with a 19 year history of heavy drinking, and recurrent episodes of jaundice, ascites and gastrointestinal hemorrhages for the past 16 years. During the night before admission, he had vomited large

amounts of bright red blood and coffee ground material. Telangiectasis and spider angiomas were noted over the face and upper trunk. The blood pressure was 138/80. The liver edge was enlarged four cm. below the costal margin at the right midclavicular line, and was described as smooth, firm and slightly tender. The erythrocyte count was 3.6 million with 71% hemoglobin, and the prothrombin time was 37%. The patient was treated with sedation, 60 mg. of Vitamin K subcutaneously, and parenteral fluids including Vitamins B and C. He continued to vomit mouthfuls of dark brown and red fluid, and his blood pressure dropped to 74/50. Fifteen hours after admission, cardioesophageal tamponade and thrombin instillation were begun. High protein feedings were given by drip. No further signs of hemorrhage were observed. The blood pressure rose to 160/88 after two transfusions. At this time the red blood count was 4.8 million with 95% hemoglobin. The balloon was deflated after 60 hours and passed into the pyloric end of the stomach. The next day the tube was removed and his further hospital stay was uneventful. During his convalescence, esophagoscopy and esophagrams could not demonstrate varicosities. An upper gastrointestinal series was normal. The patient was discharged after two months of hospitalization at which time it was considered that he had bled from a severe erosive gastritis. Three months following his discharge, the patient was readmitted in a critical condition due to an acute myocardial infarction. He expired four hours after arrival on the Reception Service.

The immediate cause of death at autopsy was found to be an anterior myocardial infarction with rupture of the left ventricular wall and cardiac tamponade due to hemopericardium. The liver showed a severe periportal cirrhosis. The portion of the autopsy protocol referring to the upper gastrointestinal tract is quoted directly: "The esophagus presents an intact wall throughout with delicate, smooth, white mucosa. There are no ulcerations. The submucosal veins in the distal third of the esophagus are not unduly prominent. In the cardiac end of the stomach, the mucosal folds are discolored blue, and sections through these areas reveal large, dilated submucosal veins. In one area of the cardia, there has been hemorrhage into the submucosa and the mucosa. The latter area, in particular, could well have served as the source of gastrointestinal hemorrhage mentioned in the clinical history. The remainder of the stomach and the duodenum reveal no areas of ulceration or erosion."

Case 3. C. M. L., a 51 year old salesman, who had been imbibing a pint of whiskey daily for at least five years, was readmitted because of abdominal distention and ankle swelling. Abdominal paracenteses had been necessary in the past, and liver biopsy and liver function tests were compatible with a periportal cirrhosis. He appeared chronically ill with many of the stigmata of hepatic disease, such as icterus, liver palms, hypotrophic testicles, spider angiomas over the upper trunk, marked ascites, and a moderately enlarged liver. While in the hospital, the patient began vomiting coffee ground material and blood clots, and had two copious, loose, tarry stools. On admission his blood count had been four million erythrocytes and 76% hemoglobin; this fell to 2.9 million with 60% hemoglobin. Tamponade of the cardioesophageal junction was begun, and continued for 72 hours, with the patient on

parenteral feedings during this period. After deflation of the balloon, the tube was slipped further into the stomach, and continuous suction was instituted. In the absence of any signs of blood in the aspirate, the tube was removed 23 hours later. The patient's red blood count at this time was 4.1 million with 79% hemoglobin.



FIG. 4. X-ray of modified Miller-Abbott tube tamponing the lower esophagus and ballooning out into the cardia of the stomach. The balloon is filled with 20 cc. of Diodrast and 100 cc. of water. Dots have been placed to outline the balloon. Case 4.

The patient had a prolonged hospital stay because of the persistent ascites, but hematemesis or melena did not recur. It is anticipated that a portacaval shunt will be performed on this patient.

Case 4. J. E. L., a 32 year old Mexican with an 18 year history of alcoholic over-indulgence, was admitted to the Brentwood Neuropsychiatric Hospital, Veterans Administration, following a prolonged drinking spree. In 1945, on a previous admission, he was considered to be a cirrhotic. An enlarged, tender liver, jaundice, ascites and ankle edema were reported at that time. Twenty-four hours after his present admission, he began vomiting dark red blood in small quantities. The liver was felt three cm. below the costal margin. After intermittent emesis of an estimated 600 ccm.

of blood, he began vomiting large quantities of coffee ground material, so that approximately 1600 ccm. was lost within three hours. The blood pressure at this time was 112/90, pulse rate was 116, and the red blood count 3.2 million with 9.8 gm. of hemoglobin. A tentative diagnosis of bleeding from a ruptured varix was made and esophageal tamponade instituted (Fig. 4). Milk was given by continuous drip, and thrombin sips administered at the rate of 1000 units every four hours. Aspiration of the stomach immediately after intubation showed fresh blood; six hours later small blood clots floating in milk were recovered. After twelve hours, the aspirate contained only bile stained milk. The balloon was deflated after 51 hours, and 21 hours following deflation the tube was removed. The patient made an uneventful recovery.

The patient was studied, after a short period of convalescence, in an attempt to determine the source of his hematemesis. The upper gastrointestinal x-rays were normal, and gastroscopic examination revealed a mild, chronic, superficial gastritis. On esophagoscopy, an area of linear prominence at the cardioesophageal junction with intensive hyperemia and granularity was found. This lesion is considered the cause of his hemorrhage.

COMMENT

When a diagnosis of severe, continuing bleeding from an esophageal varix has been made, management with tamponade and thrombin should be considered. In the previously reported cases, and in two of ours, it appeared to be the factor which prevented a rapidly fatal termination. It also seems reasonable to employ tamponade in instances where the clinical picture is not yet critical, as in our fourth case. The possibility of variceal hemorrhage is strongly suggested when other evidence of portal hypertension such as ascites, splenomegaly or dilated superficial abdominal veins exist. Liver failure, manifested by jaundice, abnormal liver function tests and hepatomegaly also supports the possibility that an upper gastrointestinal hemorrhage is secondary to ruptured varices. However, cirrhotics may also bleed profusely from an acute, erosive gastritis or a coexistent peptic ulcer. Thus, although the situation has not yet arisen in our experience, it would seem reasonable to discontinue the tamponade, if after a few hours, the patient continues to hemorrhage. Further tarry stools do not necessarily indicate fresh bleeding; the suctioned gastric contents, serial blood counts and sphygmomanometer readings are better aids in deciding whether bleeding is continuing.

SUMMARY

Four cases of massive esophageal bleeding satisfactorily treated with tamponade are presented. Our experience confirms the promising results obtained in three previously reported cases. Further details in the technique are delineated, and the instillation of thrombin solution in conjunction with esophageal tamponade is suggested.

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THE DIAGNOSIS OF CARCINOMA OF THE ESOPHAGUS: THE METHOD OF BIOPSY WITH THE RETROGRADE CURETTE

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Methods to establish the diagnosis of carcinoma of the esophagus by biopsy have acquired increased importance in recent years because of the advances in surgical technique which permit operative removal of the lesion, particularly when it is located in the lower two-thirds of the esophagus.^{1,2,3,4} In most cases, a definite diagnosis can be established by performing a biopsy through the esophagoscope. At times, however, a biopsy is unobtainable or is negative by this method. For such cases a retrograde curette designed to obtain tissue from the lower end or middle of the lesion has been devised. The present report is an evaluation of the accuracy of various methods of diagnosis of carcinoma of the esophagus in a group of patients studied at the Presbyterian Hospital. The technique of application of the retrograde curette is described.

CASE MATERIAL

During the past 18 years, 152 patients with squamous cell carcinoma of the esophagus proven histologically have been treated in the Presbyterian Hospital. In this group there were 92 white males, 32 negro males and 28 white females. Approximately one-half of the lesions were located in the middle third of the esophagus and the other half equally divided between the upper and lower thirds. Most reported series show a somewhat greater incidence in the lower third of the esophagus. Our cases were all histologically proved and it may be that some series of cases include secondary invasion of the lower esophagus from carcinoma of the fundus of the stomach, a not too infrequent occurrence which is difficult to differentiate on x-ray diagnosis alone.

The greatest age incidence was in the sixth and seventh decades; more than half of all the cases occurring in these age periods. The youngest patient was 29 years of age and the oldest was 83 years.

The commonest presenting symptom was dysphagia, which was usually more pronounced for larger particles of solid foods. This was present in two-thirds of the patients. Other prominent symptoms were pain on swallowing, weight loss and vomiting or regurgitation.

The average duration of symptoms prior to admission to the clinic was slightly less than five months. The fact that symptoms tend to occur rather late in the disease has been emphasized before⁵ and is one of the most important reasons for the poor prognosis in this disease. The survival time after the first visit was very short in some cases, averaging five and a half months.

ROENTGENOLOGICAL EXAMINATION

Roentgenological examination was carried out in all except six patients in this series. A presumptive diagnosis of carcinoma was made in 92 per cent of the patients who were examined by x-ray. In most instances this interpretation was based on evidence of an obstruction to the flow of barium. In many of the patients the normal mucosal pattern of the esophagus appeared to be destroyed and frequently a constricting filling defect was observed.

Seven patients in the group were considered to have a normal appearing esophagus on first examination. Four of these individuals were later shown to be suffering from carcinoma of the upper end of the esophagus, a region which is notably difficult to examine by x-ray methods. Only one carcinoma in the middle third of the esophagus was not seen on x-ray examination. Two of the above seven patients were found to have evidence of a lesion when the x-ray examination was repeated.

In five additional patients, roentgenological study disclosed evidence of disease but a diagnosis of carcinoma was not made. Two of these patients were initially thought to have cardiospasm, one was considered to have esophagitis and in two cases "narrowing" of the esophagus was described.

ESOPHAGOSCOPIC EXAMINATION AND BIOPSY*

One hundred and thirty-nine patients in the group were subjected to esophagoscopic examination. Usually the tumor was visualized by this method and appeared as a grayish or yellowish mass with a smooth indurated surface or a cauliflower-like protuberance, frequently ulcerated or bleeding and often constricting the lumen of the esophagus. A total of 158 esophagoscopic examinations were performed. Positive biopsies for cancer were obtained with biopsy forceps in 124 instances or 79 per cent of these esophagoscopic studies. In ten patients the procedure was carried out more than once before a positive biopsy was obtained.

Biopsies which were negative for cancer were reported in seventeen examinations. In eight of these cases normal esophageal mucosa was obtained. Five biopsies showed only evidence of esophagitis and in four instances the biopsy specimen was not satisfactory for interpretation. No biopsy was obtained on seventeen other examinations for various reasons. In some instances the lesion could not be seen or appeared to be submucosal or extraluminal. In other patients, the lesion was interpreted grossly as due to spasm or stricture. Many of these failures can be explained by the fact that the carcinoma frequently invades the submucosal tissues at the upper end of the lesion, elevating the normal mucosa. At esophagoscopy this fold of normal or inflamed edematous

* These examinations were carried out by various members of the staff of the Department of Otolaryngology.

mucosa is the tissue which may present itself and from which a biopsy specimen is at times obtained. Jackson has emphasized this particular point.⁶

RETROGRADE BUCKET CURETTE

When a biopsy was negative or unobtainable by esophagoscopy, the retrograde bucket curette was usually used. This instrument (Figure 1) consists of a hollow metal "olive" which is constructed so that the upper end presents four curetting edges. The olive is attached to the distal end of a flexible metal

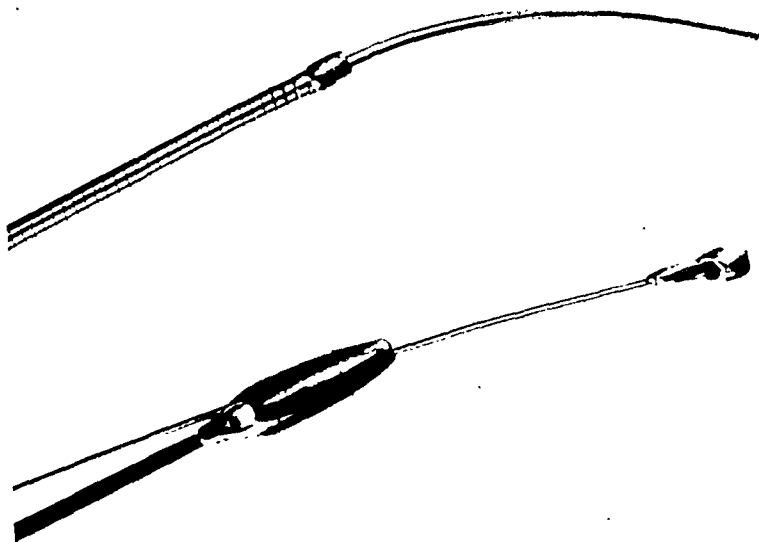


FIG. 1

Upper: Flexible hollow carrier with flexible tipped wire in place.
Lower: Retrograde curette threaded over knob-tipped wire.

staff. A hole in the curette permits it to be passed into the esophagus by threading it down a previously inserted guide wire or thread. It is believed essential that the instrument be passed along such a wire or thread to avoid unnecessary trauma. The curette is introduced into the esophagus after a guide wire has been inserted in the manner described by Crump.⁷ With the patient in a sitting position and the head hyperextended, a hollow flexible metal carrier is passed to the site of the obstruction in the esophagus, and a flexible tipped wire introduced through the lumen of the carrier (Figure 2).

The procedure then follows the steps outlined in Figure 3.

(1) When the wire reaches a point of resistance, the carrier is withdrawn a few centimeters.

(2) The flexible tipped wire is gently rotated until it finds the lumen, then gently advanced past the site of obstruction.

(3) The carrier can now also be advanced past the site of obstruction, and if further areas of narrowing are encountered, the same steps are repeated. In this manner the flexible wire is advanced into the stomach.

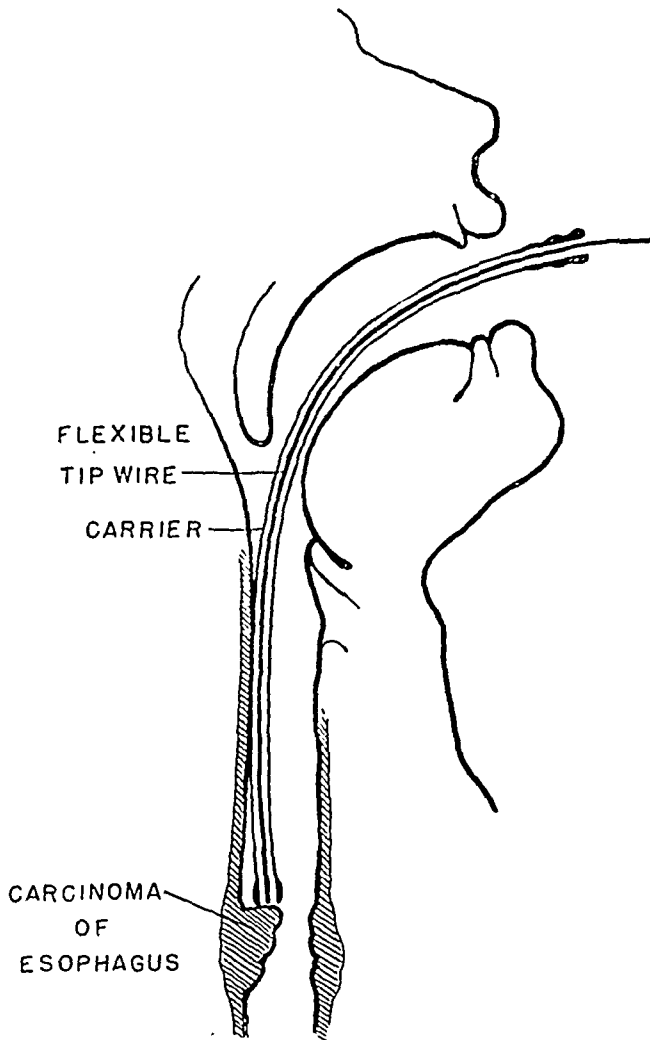


FIG. 2

(4) The carrier is withdrawn leaving the flexible tipped wire in place.

(5) A perforated knob-tipped wire is passed over the flexible wire into the stomach and the latter removed.

(6) This blunt knob-tipped wire now serves as a safe guide for other instruments, preventing perforation of the esophagus. The knob-tip will not allow the other instruments to advance beyond the end of this wire.

(7) If the lumen at the site of obstruction is too small to allow passage of the curette, graduated metal bougies can be used for dilatation.

(8) The bucket curette can now be safely passed into the stomach and then withdrawn with a sharp jerking motion enabling it to bite into and obtain tissue from the lower portion or body of the lesion.

Blind instrumentation of the esophagus should not be attempted until an x-ray examination has ruled out such lesions as diverticula, varices and aortic aneurysms, which are contraindications to such procedures.

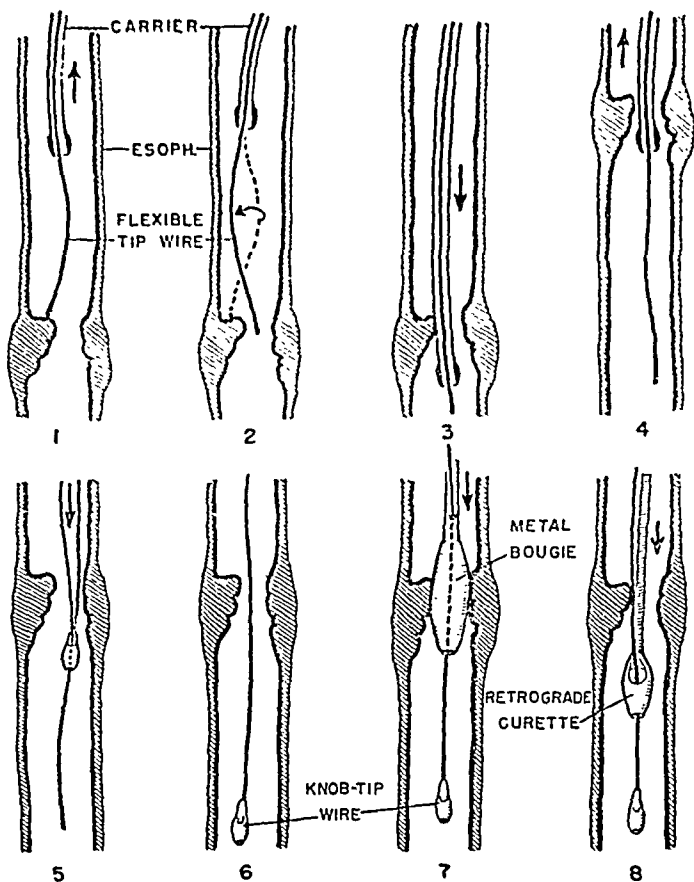


FIG. 3

When the flexible wires described above are not available* a thread may be used as a guide for the curette. A silk braid weighted with a buckshot may be swallowed by the patient and allowed to pass slowly into the small intestine as described by Plummer.⁸ The curette is introduced over the thread into the stomach and a biopsy obtained as it is withdrawn. In our clinic the silk

* The curette, the flexible tipped and knob-tipped wires, flexible hollow metal carrier, dilating olives and stiffs were specially designed for our clinic by one of us (A. B. C.) and are not at present available commercially.

thread or braid is seldom used, since we feel that a flexible wire offers a more rigid and much safer guide for the dilating olives or for the curette. In no instance did the use of the curette cause any serious reaction such as mediastinitis or hemorrhage.

RESULTS WITH RETROGRADE CURETTE

A positive biopsy specimen was obtained in eighteen of the twenty cases in which the curette was used (90%). In fifteen of the cases the biopsy was positive on the first attempt. In three of the five cases in which the first biopsy was negative, a second attempt proved successful. In the other two patients a subsequent esophageal biopsy through the esophagoscope was positive. These 18 cases include 10 in whom a previous esophagosopic biopsy had been negative, three in whom esophagoscopy had been performed but no biopsy obtained and five in whom an esophagosopic examination was not made. Two of the latter were considered too ill to undergo esophagoscopy.

DISCUSSION

In carcinoma of the esophagus, accuracy of diagnosis is of great importance. Curative therapy involves either radical surgery or radiation. An increasing number of successful resections in patients with this disease is being recorded and operative procedures have been extended to include lesions of the upper and middle thirds of the esophagus. Obviously these procedures should not be undertaken on the basis of suspicion of malignancy alone, and every effort should be made to establish the diagnosis with certainty. Roentgenological examination is highly accurate in suggesting the possibility of carcinoma of the esophagus. In the present series it was correct in 92 per cent of patients. In a small proportion of individuals, cancer of the esophagus may be overlooked on x-ray examination or may not be demonstrated. The proportion of cases in which the lesion is overlooked will be reduced if a second examination is carried out when the clinical picture is suggestive of cancer and the first x-ray study unrevealing.

Clinically and roentgenologically carcinoma of the esophagus may be impossible to differentiate from spasm or benign stricture. If the carcinoma is located at the level of the cardia, it may produce an x-ray appearance which is consistent with cardiospasm. Cancer of the lower third of the esophagus may simulate the Plummer-Vinson syndrome or so-called "esophagitis" with spasm or stricture. In our experience, some help in differentiating between those obstructions due to spasm and other obstructions is afforded by attempting to pass a large (No. 34 French) stomach tube containing a flexible metal carrier. In most patients with spastic lesions involving the esophagus, such a flexible tube will pass through the esophagus into the stomach, although the passage may be delayed temporarily at the level of spasm.

Usually histological proof of carcinoma can be obtained by biopsy taken through the esophagoscope. In the present series, a positive biopsy was secured

in 79 per cent of cases. Failures occur if the lesion cannot be directly visualized or if tissue for biopsy is removed from a region above the upper limit of the tumor.

When an esophagosopic biopsy is negative for carcinoma, the retrograde bucket curette has been of value in securing satisfactory material for histological diagnosis. In the present series, it yielded a positive biopsy in 18 of the 20 patients in which it was used, including 10 individuals on whom esophagosopic biopsies had been negative. The success of this method appears to be due to the fact that the retrograde curette renders it possible to secure a specimen from the lower part of the lesion in contrast to the esophagosopic biopsy which is usually from the upper end of the growth. Hemorrhage, mediastinitis, shock, and perforation of the esophagus have not been encountered in connection with the use of this instrument. The curette has also been of value in obtaining biopsies by the same method from patients suspected of having adenocarcinoma of the stomach involving the region of the cardia and in patients with recurrence of carcinoma following resection and esophagogastrostomy. The curette can also be used under direct vision through the open end esophagoscope.

SUMMARY AND CONCLUSIONS

1. Accurate diagnosis of carcinoma of the esophagus is becoming increasingly important as the disease becomes amenable to cure by radical surgery.

2. A review is presented of the accuracy of diagnostic methods as applied to 152 proven cases of carcinoma of the esophagus.

a) Roentgenological examination resulted in a correct presumptive diagnosis in 92 per cent of cases.

b) Biopsy obtained during esophagosopic examination was positive in 79 per cent of examinations.

3. A retrograde curette for use over a guide wire or swallowed thread is described which gave a high percentage of positive biopsies in patients on whom the diagnosis had not been proved by esophagosopic biopsy.

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MESENTERIC LYMPHADENITIS

A CLINICAL AND EXPERIMENTAL STUDY

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Mesenteric lymphadenitis, well-known to the older physicians by the name of "strumous abdomen" has attracted attention from time to time. The diagnosis was usually conjectural and recorded as an entity only when seen at autopsy. *Tabes mesenterica*, a term introduced by Bell in the early part of the nineteenth century, is now restricted to glands of tubercular origin. In 1923 Freeman¹ introduced the term "non specific mesenteric lymphadenitis" which is commonly used today. The disease usually occurs in children or young adults. It is surprising how seldom the condition is diagnosed pre-operatively. This is probably due to the uncertainty in the surgeon's mind and obviates a lengthy explanation to the parents when a diagnosis of acute or chronic appendicitis is sufficient indication for operation. Coleman² states that 35% of appendices removed following a diagnosis of acute appendicitis are normal, while the actual findings are those of mesenteric lymphadenitis. In our series 20% had normal appendices. The symptoms are often confusing, frequently mimicking many abdominal conditions, but a careful history and clinical examination should suggest the diagnosis in a high percentage of cases. This paper reports the analyses of 270 cases from the surgical services of the Royal Victoria Hospital and the results of experiments attempting to establish a virus as the causative agent.

VARIOUS THEORIES OF PATHOGENESIS

Tuberculosis has often been suggested as the etiological organism. Struthers³ believed tuberculous adenitis to be common in the young, and that the glands retrogressed. Mesenteric adenitis followed when a mixed infection was superimposed. Symmers⁴ stated that the glands were enlarged by the absorption of toxins from ulcerations of Peyer's patches in cases of intestinal tuberculosis.

McFadden⁵ found 25% of clinically non tuberculous patients harboured active tubercle bacilli in their mesenteric nodes. Heusser⁶ denied the role of tuberculosis and suggested the agency of intestinal parasites. Other etiological factors such as trauma, breaches in the intestinal mucosa and enteritis have been suggested but there is little evidence to support the claim.

Wilensky and Hahn⁷ observed in their series of cases that mesenteric adenitis was practically never seen in acute appendicitis and that in the former there were no pathological changes in the appendix. They observed mesenteric

adenitis in typhoid fever and postulated the theory that Peyer's patches were like the tonsils, and that mesenteric nodes were involved in inflammatory processes of Peyer's patches like cervical nodes in tonsillitis.

White and Collins⁸ in 1936 observed a seasonal periodicity, not unlike an epidemic of communicable disease and suggested that this was a virus infection.

The pathological and bacteriological findings have never been satisfactory. The glands showed only catarrhal lymphadenitis and the cultures were sterile or inconclusive. Heilman⁹ working in Rosenow's laboratory cultured organisms from the throats of patients found to have mesenteric lymphadenitis at operation and inoculated rabbits with the organisms. At the end of 72 hours these animals were found to have enlargement of the lymph nodes of the small intestine. He suggested that the disease could be passed from one individual to another through the naso-pharyngeal secretions similar to the epidemic forms of cervical lymphadenitis.

ANALYSIS OF CASE REPORTS

A series of 270 case reports of mesenteric adenitis, diagnosed at operation were analysed. These were all cases operated upon at the Royal Victoria Hospital between 1930 and 1946.

The ages were between five and fifteen, almost equally divided between the sexes. A correct pre-operative diagnosis was only made in 10% of the cases.

Pain. This was generally the first symptom. In the acute cases it closely resembled appendicitis starting in the paraumbilical region and later localizing to the right lower quadrant. On palpation tenderness was present in this area in 85% of the cases. Many of the histories described the tenderness as being about one inch below and to the right of the umbilicus, often referred to as "Land's Point". Klein's test, which simply means palpating the abdomen with the patient lying on the left side, so that the mesentery may fall to the left shifting the point of tenderness to this area was not carried out in this series. About one-third of the cases could be described as acute. The remainder were the chronic cases whose symptoms varied from one to ten months. The pain was described as coming on at irregular intervals. Often the child would be having a meal, complained of pain, occasionally vomited, but after resting for a short time would feel well again. Several became nauseated at school, complained of pain and were sent home, but by the time they arrived the attack had passed. The pain occasionally occurred at night and sometimes when the patient was mentally disturbed, or wished to avoid certain unpleasant duties. Nausea and vomiting were observed in 75% of the cases and diarrhea or constipation in 55%. The temperature was only slightly elevated, never exceeding 102 by rectum and the pulse moderate. The white blood count varied from six to fifteen thousand and with a relative lymphocytosis in the few cases where differential counts

were carried out. Cervical adenopathy was present in 20% of the cases and in only a few cases could glands be palpated in the abdomen. 20% had an associated naso-pharyngitis, tonsillitis, or otitis media. 25% had had a previous appendectomy. There were no cases of suppuration.

Appendectomy was carried out in 97% of the cases. In this series 62% of the appendices removed showed chronic inflammatory changes histologically; 15% showed acute exudative changes; 20% had normal appendices, which were removed; all had enlarged and reddened mesenteric nodes. 7% of the appendices showed evidence of oxyuris vermicularis. Meckel's diverticulum uninflamed, was seen in three cases.

A biopsy of a mesenteric gland was done in ten per cent of the cases. Pathologically, catarrhal lymphadenitis was the characteristic finding. In two cases, *Corynebacteria Hoffmani* and *Enterococci* were grown; but these could well be considered as contaminants, as all the other cultures proved negative. 3% showed abdominal fluid, culture of which also proved negative. No cases of suppurating glands were found.

Follow-up on these cases were difficult. In all, 92 cases were located by mail. In these 75% were cured, with great improvement in general health. Twenty-one complained of a recurrence of similar abdominal pain one year to six years after the operation. All were eventually free of attacks.

Experimental Results

The experiments reported below were planned as an attempt to establish the presence of a virus in the glands. The glands were extracted and injected directly into the subserosal area, and mesentery, in monkeys and into the peritoneum, and brains of rats and mice.

Methods. One or more mesenteric glands were removed at operation from each of thirteen humans found to have mesenteric lymphadenitis. One portion was fixed in formalin and sectioned. Another was cultured aerobically and anerobically. The remainder of the material was transferred to a mortar and ground with sand under sterile conditions. Distilled water was then added and placed in a refrigerator for 24 hours. It was then passed through a Berkfeld filter and the filtrate used as the infecting agent.

Four *Macacus Rhesus* monkeys, seventy-two mice and twenty-four rats were used. General anesthesia was used for the monkeys and the rats, throughout all the procedures. None was used on the mice. The abdominal walls of the monkeys were carefully shaved and prepared with alcohol and zephiran. Subumbilical midline incisions were used as these would afford adequate exposure of the ileo-cecal region as well as the mesentery. The terminal ileum and the cecum were easily delivered into the wound, and the mesentery inspected for any obviously enlarged glands. Only a few slightly enlarged nodes

were found in the monkeys along the medial border of the cecum. The animals were inoculated with the prepared filtrate, using a fine hypodermic needle. In the first monkey, several drops of the filtrate were introduced between the leaves of the mesentery of the small intestine, starting about one inch from the ileocecal region and using five or six areas at intervals of about one inch just beyond the arterial arcades.

In the second monkey, the injections were made subserosally in a manner quite similar to the first.

In our third case, we used a combined method, injecting both subserosally and into the mesentery.

The fourth animal served as a control. Here we used normal saline and gland filtrate from the mesentery of a presumably healthy person, to eliminate the possibility of a sensitivity reaction of the monkey to the foreign protein in the human gland filtrate.

The rats were treated in a similar manner. Control experiments here consisted of injecting the mesentery with saline; and in simple laparotomy.

Mice were injected intracerebrally and intraperitoneally without any anaesthesia. These animals were sacrificed on the tenth day, and in the case of the intracerebral method, the brains were removed and saved for microscopical section, and in the case of the intraperitoneal method, the mesenteric lymph chain was removed and examined microscopically after being fixed in formalin.

The post-infection course in each case was uneventful. Each abdomen of these animals was inspected ten days after the inoculation. Special note was made at this time of the appearance of the mesenteric nodes, and specimens were taken for pathological and bacteriological examinations.

Transmission experiments were also carried out using the infected mesenteric gland of rats. These rat glands were crushed and treated as were the human glands and then filtered. The filtrate was then used to inoculate new rats and mice intracerebrally and intraperitoneally; and the results recorded.

Experimental Results. Monkeys—The abdomens were opened under sterile conditions two weeks after the injections. There was an increase in the number of mesenteric nodes but section showed only catarrhal changes with no evidence of an acute inflammatory process.

Rats—Nine animals were used as controls, with simple laparotomy. After ten days no change was noted in the mesenteric glands.

Five rats were inoculated into the mesentery and subserosa of the terminal ileum. After two weeks the abdomens were opened and a mild adenopathy was noted. Section of these nodes showed no acute process.

Five rats were inoculated in a similar manner and at the end of two weeks the glands were removed and a filtrate prepared as described above. This was injected into the mesentery of five fresh rats. After two weeks the mesenteries showed nothing remarkable.

Mice.—Twenty-four animals were injected intraperitoneally with the human gland filtrate. All survived and were sacrificed on the tenth day and the lymphatic chains removed. Nothing remarkable was seen. Germinal centres and endothelium were normal. No acute lymphadenitis was seen.

Forty-two animals were injected intracerebrally using 0.05 cc. of the filtrate. Two died on the third day but the brains appeared normal at autopsy. The remainder were sacrificed on the tenth day. The brains were all saved for study. Cultures were negative. Microscopic sections revealed no meningitis or encephalitis. There was perivascular cuffing. A diligent search was made for inclusion bodies but none were found.

Discussion of the Clinical and Experimental Results

From the observations made on the clinical cases, it would be unjustifiable to class this condition as an enteritis; for at operation, it was found that the glandular enlargement was constant whereas any evidence of inflammatory changes in the bowel were exceptional.

The appendicular origin of non-specific mesenteric adenitis as suggested by Foster¹⁰ (1938) and Adams and Olney¹¹ (1938) is difficult to substantiate, when we recall that in the cases studied, the juxta-ileal glands were the ones that were predominantly and invariably enlarged in early cases of adenitis. This group of glands is not usually involved in appendicular infection as noted by Wilensky and Hahn,⁷ unless perforation and peritonitis have supervened. The appendicular lymphatics drain to the ileo-colic glands, and thence direct to the terminal superior mesenteric group of glands.

Appendectomy is specifically recommended by some. Foster¹⁰ claimed that if appendectomy was performed, patients seldom reported a return of the pain, after operation; but that those treated conservatively usually complained of recurrence. However, as Aird¹² points out, this argument is inconclusive, because abdominal pain is always regarded more anxiously by the child's parents if the appendix is present than if the appendix has been removed. Rosenberg¹³ (1937) pointed out that two-thirds of the patients treated by appendectomy for non-specific mesenteric adenitis do, in fact, have a recurrence of the pain after operation; we found that 22% of those treated by appendectomy had a recurrence of the pain in the abdomen, but only 35% of the cases were heard from in the follow-up carried out. Sobel and Stetton¹⁴ report that two-thirds of patients seen in the first attack have recurrence if the operation is withheld, and believe that appendectomy has some relation to the cure of this disease. In this series of fifty-eight cases, forty per cent had appendicular adhesions.

No comment can be made on the suggestion of Felsen¹⁵ (1935) that organisms of the dysentery group might be responsible, because no stool or blood agglutination studies were carried out.

CONCLUSION

Non-specific Mesenteric Lymphadenitis is a clinical entity that should be diagnosed with reasonable certainty.

The etiology is still obscure and our animal experiments do not show a virus as the infecting agent.

No fatal case has ever been observed and it appears to be a self limited disease. Appendectomy, however, seems to have a beneficial effect on the course of the disease.

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Case Reports

JULIAN RUFFIN, M.D.

Durham, N. C., Associate Editor in Charge

BENIGN ULCER OF THE GREATER CURVATURE OF THE STOMACH (REPORT OF A HISTOLOGICALLY PROVEN CASE)

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INTRODUCTION

Histologically proven cases of benign peptic ulcer on the greater curvature of the stomach are uncommon. A careful review of the literature revealed only twenty such cases reported to date¹⁻¹⁶ (Table 1). It is impossible to accept many of the alleged cases because of the lack of histologic evidence. In the twenty cases reported, no characteristic syndrome was present.

The purpose of this paper is to describe an additional histologically proven instance.

CASE REPORT

ES (277680), a 23 year old male was seen on 2-19-48 complaining of "stomach trouble" since 1939. His distress was characterized by belching and vague generalized pain occurring periodically, usually soon after meals. These symptoms continued unchanged until September 1947, when the distress became more severe and was associated with a sensation of heaviness in the abdomen. These symptoms occurred at irregular intervals, usually daily, and now appeared both before and after meals. Food would occasionally aggravate the pain; relief sometimes would follow a bowel movement. Throughout this period, the patient's appetite was good. There was no loss of weight, nausea or vomiting. Bowel habits were normal with no bloody or tarry stools.

The past history was essentially negative. The physical examination was normal. Laboratory tests were as follows: RBC 4.02, Hb 13.5, WBC 8,200; the differential white blood count, normal. Examination of the urine was negative. The histamine test revealed a maximum free acidity of 118 in the 30 minute specimen. Two continuous twelve-hour fractional night secretion studies were done on two consecutive nights. Each revealed continuous secretion of copious amounts of free hydrochloric acid. Roentgen examination on 2-23-48 (Figure 1) disclosed a deformity with at least one, and possibly two small craters on the greater curvature of the antrum. There was some stiffness in the region; the mucosal folds were obliterated. The final roentgen impression was that of an ulcerating neoplasm. A second examination confirmed the original findings. The gastroscopic report on 3-24-48 (J. B. K.) was as follows: "The angulus and entrance to the antrum was clearly seen. On the greater curvature of the antrum, there was a definite ulceration (1.5 cm. in diameter) which appeared to be

TABLE 1
Benign ulcers of greater curvature of stomach
(Proven Histologically)

AUTHOR	YEAR	NO. OF CASES
Finsterer.....	1914	1
Podlaha.....	1923	1
Lorenz.....	1924	2
Simon.....	1927	1
Sladsky.....	1928	2
Koch.....	1928	1
Sommer.....	1924	1
Matthews.....	1935	2
Van Buchem.....	1938	1
Williams.....	1941	2
Preis.....	1944	1
Blum.....	1944	1
Hussar.....	1947	1
Gobeau.....	1947	1
Campbell.....	1948	1
Cave.....	1948	1

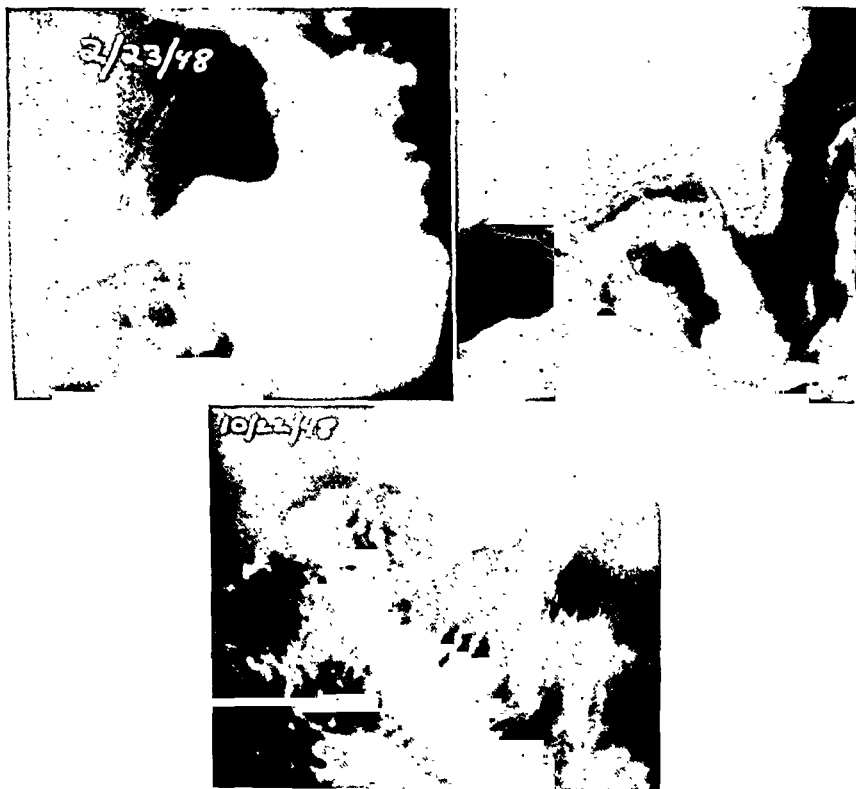


FIG. 1. February 23, 1948 and March 19, 1948: Ulcer crater on Greater Curvature of Antrum with Surrounding Edema. October 22, 1948: Examination seven months after operation Demonstrating a Normal Gastroenterostomy.

situated on an elevation with surrounding nodularity. The margin could be followed in only three fourths of its circumference; there was a bloody discharge flowing over

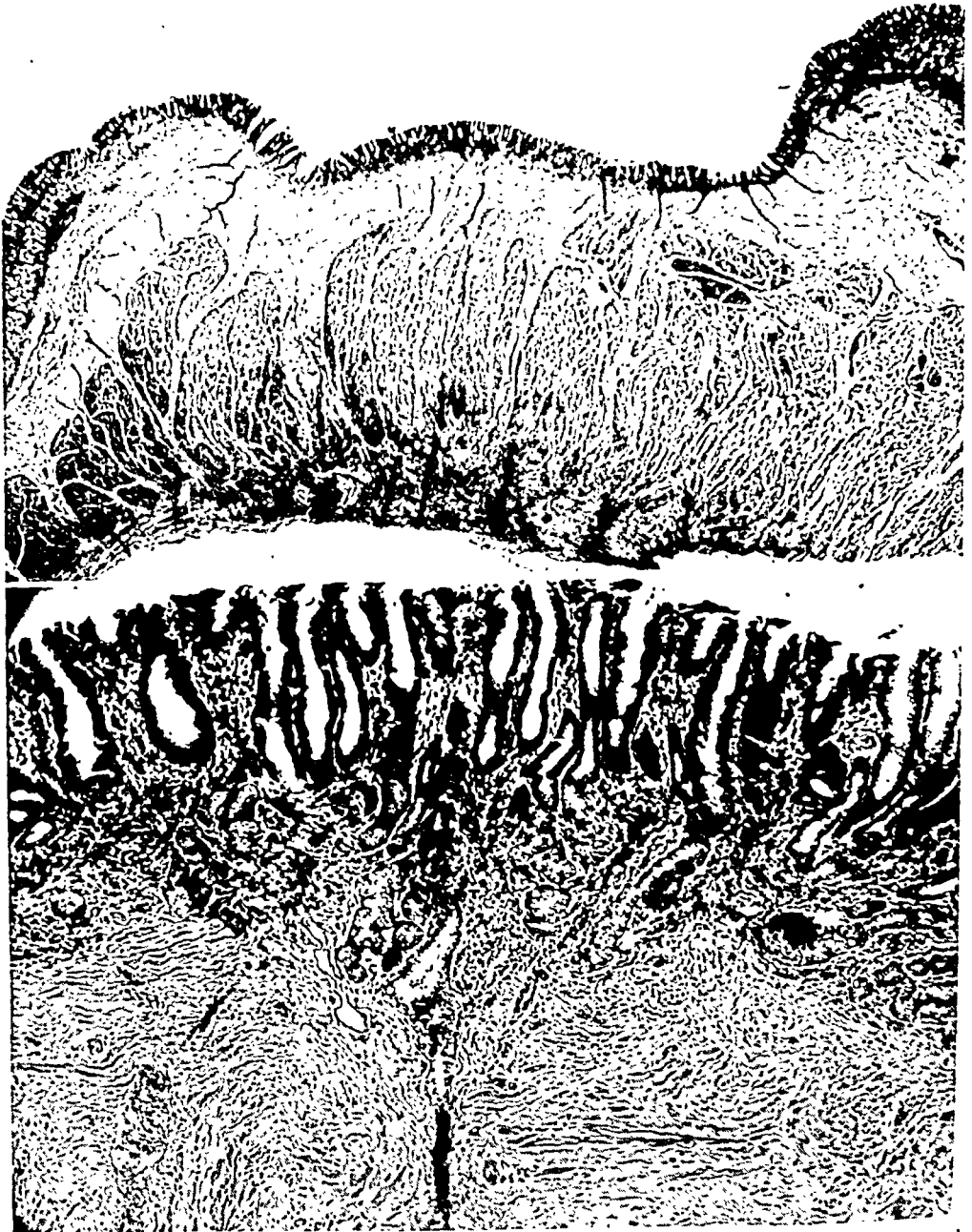


FIG. 2. Photomicrograph Magnification (a) $\times 13$ (b) $\times 120$ Illustrating the Healing Benign Gastric Ulcer.

the remainder. Proximal to the ulceration there was a persistently adherent large blood clot. The ulcer did not remain in the visual field for more than a few seconds at a time due to the movement of the antrum. The pylorus was not looked for, nor did it come into view. The mucosa elsewhere in the antrum appeared fairly normal.

In view of the location of the ulcer, the adjacent nodularity, continued bleeding and failure to see a complete border, the lesion must be regarded as malignant."

The patient was subjected to a subtotal gastrectomy by Dr. Dwight Clark on April 6, 1948. On the greater curvature, 2.0 cm. proximal to the distal line of resection, there was a partially healed, oval ulcer measuring 2.0 x 1.2 cm., the center of which was depressed 1 to 2 mm. The edges were sloping; the center of the ulcer was covered by smooth hyperemic tissue which appeared grossly re-epithelialized except, possibly, at one margin. Here there was a depressed, apparently unhealed portion, 8 x 2 mm. The floor of the ulcer contained a grayish exudate. The edges and the base of the ulcer were slightly firmer than the surrounding gastric mucosa but were nowhere hard. For 2 to 3 cm. surrounding the ulcer the rugal folds were flattened and the mucosa was pale. The folds were prominent elsewhere along the greater curvature. The lymph nodes were firm and small.

Microscopic sections through various parts of the lesion disclosed a benign ulcer in a healing phase (Figure 2). A mild diffuse gastritis was evident near the proximal line of resection and at the pylorus. The regional lymph nodes were normal.

The final pathological diagnosis was "an unusual healing stage of a benign peptic gastric ulcer in an unusual location."

The patient was last seen on 1-17-49, nine months after operation. Except for failure to regain his pre-operative weight, he had no complaints. Roentgen examination disclosed a well-functioning gastroenterostomy with no evidence of recurrent ulcer (Figure 1).

SUMMARY AND CONCLUSIONS

A benign ulcer of the greater curvature of the stomach is described. The roentgen and gastroscopic characteristics of the lesion were compatible with that of a malignant lesion. The diagnosis was established by histologic examination. To date, only twenty-one histologically proven benign gastric ulcers have been described in the literature. No definite clinical criteria exist to differentiate these ulcers from carcinoma.

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RUPTURE OF THE ESOPHAGUS FOLLOWING SEVERE VOMITING

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Rupture of the esophagus following severe vomiting is observed only rarely. It is still rarer in the absence of external trauma or malignant disease. It is our purpose in reporting this case to call again to attention that the esophagus may be the site of inflammatory reaction and acute ulceration in a patient with duodenal ulcer, and that rupture of the esophagus may occur in such an individual following severe or prolonged vomiting.

PRESENTATION OF CASE

Present Illness: The patient, a 74 year old white man, was admitted to the Montana Deaconess Hospital on April 6, 1948, because of progressive swelling of his neck and shortness of breath. He had been ill for about a week with nausea and vomiting associated with epigastric pain. He also had pain in the left lower chest, posteriorly, aggravated by deep inspiration. He had been unable to sleep the night before admission because of the severity of the pain. Dyspnea developed. His vomiting became more and more severe and the enlargement of the neck was first noticed at this time, several hours before admission to the hospital. He had had recurrent attacks of epigastric pain associated with vomiting during the past several years, but had never consulted a physician for this condition.

Physical Examination revealed an acutely ill 74 year old man who was dyspneic, cyanotic, and dehydrated. His temperature was 99.4 degrees (rectal); pulse 96, and respirations 34 per minute. Blood pressure was 70/50. The tissues of the neck appeared full but were soft and crepitant on palpation. The crepitant area extended around to the back of the neck and almost up to the occiput. There was dullness to percussion over the lower portion of each side of the chest posteriorly, and to a lesser extent anteriorly. Cardiac size appeared normal to percussion except where it merged with the dullness over the lower portion of the chest. The heart tones were distant. A pleuro-pericardial friction rub was easily heard to the left of the lower sternum. There were no palpable abdominal organs or masses, and no tenderness. The extremities were normal except for the cyanosis.

Laboratory examinations: A urine specimen was not obtained. Hemoglobin was 18.2 grams per 100 c.c., erythrocyte count 5,650,000, leukocyte count 7,750, of which 65 per cent were polymorphonuclears, 19 per cent lymphocytes, and 16 per cent monocytes. Blood urea nitrogen was 38.3 mgm. per 100 c.c. Blood Wassermann was negative. Bedside roentgen examination of the chest revealed a moderate hydro-pneumothorax on the left and a marked hydrothorax on the right. Subcutaneous emphysema was demonstrated in the tissues of the upper thoracic and cervical regions.

The diagnosis on admission was mediastinitis with mediastinal and subcutaneous

cervical emphysema, bilateral hydrothorax and left hydropneumothorax, all of which, in turn, were believed to be the result of prolonged vomiting. A chronic duodenal ulcer was suspected because of the history.

Clinical course: Treatment consisted of the administration of penicillin and streptomycin intramuscularly, and sulfadiazine intravenously. A stomach tube was inserted through the nose. Five per cent dextrose in water and in physiological saline was administered intravenously. Oxygen did not appreciably improve his cyanosis or air hunger. Thoracentesis performed on the left resulted in the aspiration of 900 c.c. of a cloudy brown fluid, and approximately 200 c.c. of air. This procedure was repeated on the right, and about 800 c.c. of a similar but bloody fluid was removed. Analysis of the fluid obtained from the left pleural space showed it to have a specific gravity of 1.013; there were 3,250 cells per c.mm., of which 87 per cent were polymorphonuclears, 11 per cent lymphocytes, and 2 per cent monocytes. No bacteria were present in the direct smear or on culture. The fluid was then filtered and titrated with 0.1 N sodium hydroxide, as for a gastric analysis. There was no "free acid," but a "total acidity" of 30 degrees was found using phenolphthalein as the indicator.

The bilateral thoracentesis was followed by a short period of improvement of the patient. The cervical subcutaneous emphysema appeared to lessen and his color improved. Epinephrine and other supportive measures afforded little benefit. His temperature rose to 102 degrees (rectally). He became progressively weaker and died 20 hours after his admission to the hospital.

Necropsy examination: Only the pertinent findings will be recorded. The subcutaneous crepitation described above was present. The left pleural cavity contained about two liters of cloudy flocculent brown fluid. The left lung was markedly atelectatic. The pleural surface on the left was dull and slightly hemorrhagic, and covered with brown, mucoid flocculent material. The mediastinum was crepitant and contained a moderate amount of gas. The right pleural cavity contained about a liter of cloudy reddish-brown fluid. The pleura on the right was smooth and glistening and only slightly congested.

On reflecting the left lung, a large, posterior, mediastinal bulging mass was found. This measured 7 by 6 by 3 cm. In the upper part of this mass there was an irregular opening near the hilus of the left lung from which dark brown flocculent fluid escaped. When pressure was exerted upon the stomach, gas escaped through this same opening. On further dissection, a sharply circumscribed, longitudinal, slit-like perforation, 3 cm. in length, was present on the left posterior aspect of the esophagus, at a point about 2 cm. above the cardia. Little gross inflammatory reaction was present about the edges of this perforation, which opened into the large mediastinal mass described above. The brown fluid present in the mass apparently had ruptured the parietal pleura anteriorly, to communicate with the left pleural cavity. There was no evidence of communication with the right pleural cavity.

The mucosa of the distal half of the stomach was markedly congested and hemorrhagic. There was scarring about the pylorus, and there were two small, scarred, partially-healed duodenal ulcers immediately distal to the pylorus. One of these, the

base of which was adherent to the underlying pancreas, measured 0.6 by 0.5 cm. The other, on the superior wall of the duodenum, was 0.5 cm. in diameter.

Microscopic examination: Lungs. The outstanding feature was the marked amount of amorphous material on the surface of the pleura of the left lung. This contained vegetable fibers and mucus stained with bile. There were marked numbers of polymorphonuclear leukocytes, and some blood pigment, as well as corresponding inflammation of the superficial portion of the adjacent lung. The pulmonary tissue was

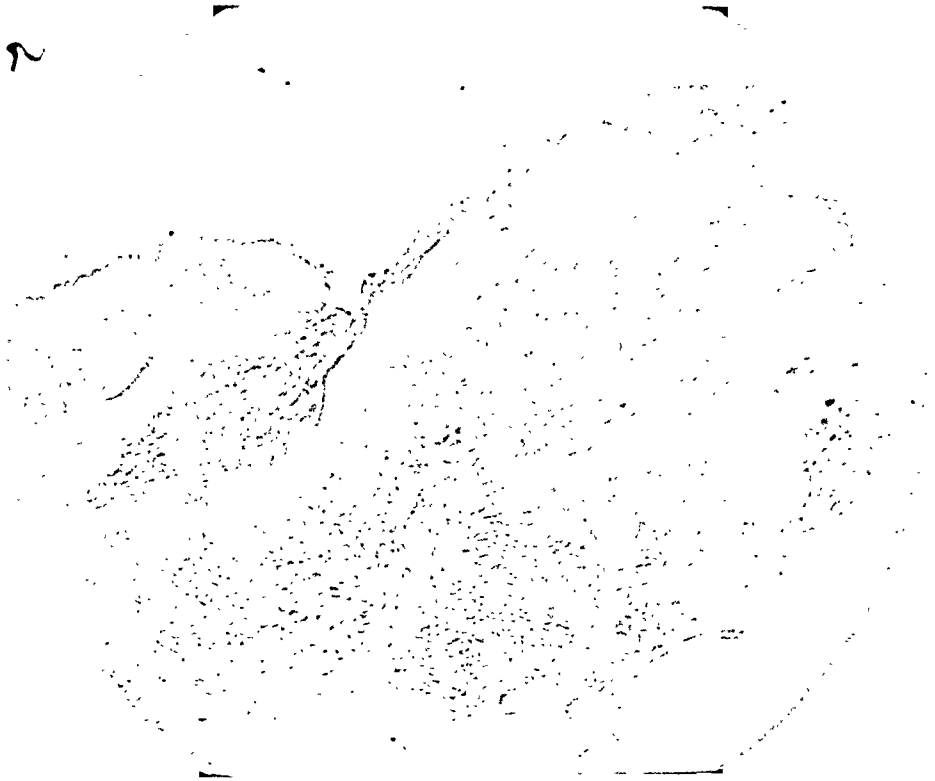


FIG. 1. PHOTOMICROGRAPH ($\times 10$) OF THE ACUTE ESOPHAGEAL ULCERATION WHICH EXTENDED THROUGH THE MUSCULARIS, LEADING TO PERFORATION OF THE ESOPHAGUS

atelectatic, but without active pneumonitis. There was slight polymorphonuclear leukocytic infiltration immediately beneath the visceral pleura of the right lung.

Esophagus. The mucosa of the esophagus at its junction with that of the stomach appeared normal. The gastric mucosa, on the other hand, revealed rather marked autolysis. As one proceeded superiorly, an ulcer of the esophageal mucosa was found extending into the muscularis. This ulcer was acute as evidenced by marked tissue destruction and polymorphonuclear leukocytic infiltration. The area of ulceration extended to the point of rupture. Externally, at the point of rupture, there was much detritus and polymorphonuclear infiltration adjacent to the muscularis.

DISCUSSION

A classical description of rupture of the esophagus following severe vomiting was reported by Dryden¹ in 1794. In his patient, the vomiting followed ex-

cessive drinking of alcoholic beverages the previous night, and was further aggravated by the ingestion of large amounts of warm water, in a deliberate attempt of the patient to produce further vomiting and evacuation of the stomach. Autopsy revealed rupture of the esophagus "before it passes into the



FIG. 2. PHOTOMICROGRAPH ($\times 100$) OF THE EDGE OF THE ESOPHAGEAL ULCER

diaphragm." Dryden warned against the injudicious use of emetics, believing that they caused more deaths of this type "than most practitioners are aware of."

Butt and Vinson^{2, 3} concluded, from their thorough study of inflammatory lesions of the esophagus, that the development of esophagitis and esophageal ulceration are distinctly favored by the act of repeated vomiting and the presence of increased acid gastric secretion. Benign stricture of the esophagus has been reported as a complication of duodenal ulcer.^{4, 5} Thus, one may observe the production of acute mucosal ulceration and subsequent cicatricial constrict-

tion. Although the esophagus plays only a passive role in the act of vomiting, rapid dilatation and excessive movement occur in an effort to aid in the elimination of the material being regurgitated. In the presence of acute esophageal ulceration, the mechanical factors of stretching occasioned by severe vomiting may easily lead to rupture, especially in an older individual.

Vomiting, however, is not a requisite for esophageal rupture. Hertzog and Leighton⁶ reported three patients who had spontaneous rupture of the esophagus. The rupture had occurred at the site of an acute ulcer of the lower esophagus, located immediately above the diaphragm. Two of the three patients had had chronic duodenal ulcers. The ages of the patients were 67, 73, and 70 respectively.

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LEUKOPLAKIA-KERATOSIS OF THE ESOPHAGUS ASSOCIATED WITH ESOPHAGEAL STRICTURE

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In leukoplakia, keratosis or hyperkeratosis of the esophagus, there is a proliferation of the squamous cell epithelium. It produces a localized thickening, a slight elevation of the surface or a warty-like growth. According to Starr, leukoplakia is a common autopsy finding. He believes that if a thorough examination is made of the terminal two inches of the esophagus many cases of non-obstructing leukoplakia would be found. As far as can be ascertained a survey of the literature, with the exception of Starr's report, reveals no other recorded cases of stricture associated with this condition. The association of stricture with leukoplakia-keratosis is very rare. Starr reported 3 cases of hyperkeratosis of the esophagus. He pointed out that it never occurred to him that leukoplakia would cause symptoms.

The etiology of this condition is unknown. Starr found that his patients were fond of very hot tea, suggesting that hot drinks may be a causative factor. The cause of the esophageal stricture cannot be explained by the leukoplakia alone, the presence of a small elevation or small growth. It is quite possible that since in our case there were definite localized inflammatory changes, that the stricture may be due to a localized esophagitis and spasm.

The roentgen appearance of the stricture is one showing benign characteristics, namely, a smooth end and a tapering esophageal lumen. In our 1 case and in Starr's 3 cases there were signs of stricture. The degree of obstruction varies. In our case it was partial, but in Starr's 3 cases the obstruction was marked.

The following case is presented:

Female, aged 49 was referred to me by Dr. M. B. Levin. She had difficulty in swallowing for one year. The dysphagia was more pronounced after swallowing solids. There were episodes of vomiting after eating and considerable loss of weight. Roentgen examination revealed a stricture of the lower esophagus, about two inches above the diaphragm. The lower esophagus tapered toward the cardia end. The lumen above the stricture showed slight dilatation. The stricture was localized and smooth, and no intrinsic lesion was noted in the x-ray to account for the stricture. She was admitted to the Mercy Hospital for esophagoscopy examination. The esophagoscopy was done by Dr. Waitman T. Zinn. At this examination a stricture was found in the lower third of the esophagus as shown by the x-ray. The stricture was dilated so that the esophagoscope could be passed beyond it. A small flattened warty-like growth was observed and a segment of this growth was removed. The following pathological report of the biopsy specimen was made by Dr. Walter C. Merkel. Microscopic description of the biopsy removed from the esophagus showed a markedly thickened

mucosa, due for the most part to a marked thickening of the superficial hyperkeratotic layer. There was a marked epithelial keratosis. The supporting connective tissue was infiltrated with mononuclears and contained lymphoid stroma. The pathologic diag-



FIG. 1



FIG. 2

FIG. 1. ROENTGENOGRAM OF THE ESOPHAGUS SHOWING A STRICTURE IN THE LOWER END AT ARROWS

FIG. 2. SPOT FILM CLOSE-UP VIEW OF THE ESOPHAGUS
The stricture and the characteristic tapering end are shown.

nosis was keratosis and chronic inflammation. The final diagnosis was esophageal stricture associated with leukoplakia-keratosis with chronic inflammatory changes. The growth was fulgrated and after several esophagosopic examinations it had



FIG. 3. PHOTOMICROGRAPH OF THE BIOPSY SPECIMEN OF THE WARTY-GROWTH

Note the thickening of the squamous cell epithelium, and the inflammatory mononuclear infiltration.

entirely disappeared. The patient has had no further esophageal symptoms and is quite well.

It appears that the condition occurs mostly in females. Starr's 3 cases and our case were females. The ages in the 4 cases ranged from 47 to 59 years.

SUMMARY

An unusual case of leukoplakia-keratosis of the esophagus associated with stricture is presented. The causative factor producing the stricture was probably due to a localized esophagitis and spasm.

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A BRANCHIAL FISTULA OF THE PYRIFORM SINUS--REPORT OF A CASE

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Remnants in the adult of the fetal branchial system in the form of cysts and fistulae are relatively rare. Embryologists refer to them as "cervical cysts and sinuses".^{1,2,3} Hyndman and Light¹ reviewed the embryology and anatomy of the branchial arches, clefts and pouches and their derivatives in 1929, and presented ninety cases of symptomatic branchial cysts and fistulae from the literature and eighteen cases of their own.

Briefly, branchial cysts and fistulae are remnants of the branchial diverticula and of the gill slits which are sometimes formed in the four to six-week fetus during the short life of the branchial system before its differentiation into the varied and disassociated structures which are its representatives in the adult. They result from the failure of absorption of endoderm and ectoderm buried during the growth and fusion of the branchial arches. Wenglowski⁵ believed they may arise along the thymic stalk as well.

Branchial cysts and fistulae may occur everywhere there is a derivative of a branchial arch, pouch or cleft from the ear to the mediastinum. There is a dispute as to whether they may arise from more than one segment of the branchial system. They occur most frequently in the pre-auricular area, the region of the lingual and palatine tonsils, and in the pharynx at the level of the hyoid bone. The fistulae are complete or incomplete and open either internally or externally. Fistulae are frequently bilateral. They are lined with epithelium of either endodermal or ectodermal origin. There is some evidence that their occurrence is familial in some instances.⁴

In a large series (Hyndman and Light¹) fistulae were present more frequently on the right as in the case presented here, while cysts were predominantly on the left. Both cysts and fistulae are usually asymptomatic until infected or distended with food or secretions. Symptoms often arise following tonsillectomy.

An incomplete branchial fistula of the right pyriform sinus was an incidental finding in a patient in Barnes Hospital.

Case Report: G. R. H.—68 year old white male.

The patient entered Barnes Hospital with the chief complaints of intermittent claudication and ankle edema of one year's duration and a chronic ulcer of the left foot of six month's duration. A diagnosis of arteriosclerosis obliterans was made.

During the course of hospitalization the patient developed nausea and epigastric pain. Examination of the stool for occult blood yielded a two-plus guaiac test and a gastrointestinal series was ordered to help rule out a bleeding gastrointestinal lesion.



(a)



(b)

FIG. 1a. ANTERO-POSTERIOR VIEW OF THE PHARYNX SHOWING RELAXED VALLECULAE AND FISTULA TRACT EXTENDING INFERIORLY FROM THE RIGHT PYRIFORM SINUS

FIG. 1b. RIGHT LATERAL VIEW OF THE PHARYNX SHOWING THE ANTERIOR EXTENT OF THE FISTULA



FIG. 2. ANTERO-POSTERIOR LAMINAGRAM OF THE PHARYNX AFTER REPEATED EMPTY SWALLOWING SHOWING THE OPENING OF THE FISTULA INTO THE PYRIFORM SINUS

Specific questioning before and after fluoroscopy revealed a vague history of occasional fullness in the neck after eating and some regurgitation of unchanged food. These symptoms were of indefinite duration. Family history and past history were non-contributory.

At fluoroscopy the barium meal was seen to enter and fill the hypopharynx in normal fashion. The left pyriform sinus stripped with each swallow but the valleculae and the right pyriform sinus were relaxed and remained full even after empty swallowing. In the antero-posterior position, the right pyriform sinus was narrow distally, abnormally long, and was seen to extend sharply toward the midline (Fig. 1a). In the oblique and lateral projections, a blind fistula was noted extending from the inferior tip of the pyriform sinus. Club-shaped in the lateral projection, the fistula tract was narrow proximally with a rounded and dilated distal portion (Fig. 1b).

Plain films of the neck and laminagrams of the pharynx and larynx revealed no abnormalities. Laminagrams of the pharynx with barium mixture in the right pyriform sinus and fistula showed the fistula extending directly from the distal tip of the sinus (Fig. 2). The remainder of the gastrointestinal tract was essentially normal.

Esophagoscopy revealed a small opening in the wall of the hypopharynx to the right of the midline anteriorly at two o'clock corresponding to the x-ray findings of the site of the fistula. The opening was too small to insert the instrument. No other abnormality was noted.

Because of the patient's age and debility and lack of serious symptoms related to the fistula, excision was contraindicated.

SUMMARY

An internal pharyngeal fistula is described. Symptoms were minimal, and the fistula was an incidental finding during routine gastrointestinal fluoroscopy. The fistula was considered a developmental anomaly of the fourth branchial segment from which rise the pharyngeal muscles and the pyriform sinuses.

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Even more striking is the fact that if one half of a part of the pallium is removed, and the cat's fur is stroked on that side, he will become a spitting, fighting beast, whereas if he is stroked on the other side he will purr with pleasure.

These observations are of great interest to physicians because so often the family of a man with cerebral arteriosclerosis and the loss of some function in the cerebrum will complain about the change in character and temperament with a tendency toward irascibility. Because of this, an old parent or grandparent can become a great problem in the home.

At the 1948 meeting of the National Academy of Sciences, reported in the May 7, number of *Science*, page 457, Philip Bard and Vernon B. Mountcastle reported studies in which they removed parts of the brains of cats. In them a condition of extreme placidity was produced by removal of all the neocortex, while at the same time sparing the remainder of the forebrain. Animals treated in this way always failed to show any sign of anger when subjected to rough handling. On the other hand, cats deprived of the entire forebrain tended to display rage on slight provocation. Apparently, in the absence of the neocortex, one or more parts of the remaining forebrain must continuously exert a calming influence upon the mechanisms in the lower portions of the brain, perhaps the hypothalamus and midbrain, which are "executively involved" in the bodily expression of anger.

Conversion of the state of placidity to one of ferocity was effected by removal on both sides of either the cortex of the midline or certain parts of the so-called olfactory brain. These studies have already had an influence on brain surgeons, who are now removing part of the neocortex of men and women to produce calmness and lack of worry. Early reports indicate that this operation gives all the good results of prefrontal lobotomy without so many of the bad results. Further contributions on the subject will be watched with interest.

It would seem that these observations have immediate clinical value. Recently Heath and Pool (*Psychosom. Med.*, 10: 254, 1948) reported the results of operations on 24 chronic psychotic patients who had not responded to conventional treatment. The surgeons removed small bits of the frontal lobes corresponding to areas 9 and 10 on the Brodmann map. After this operation the patients did not develop "the tactlessness, irresponsibility, and lack of remorse that so frequently follow the conventional lobotomy." The new operation is called topectomy. Heath and Pool now have 10 patients who are able to "function at their old capacity." In these cases rage, fear and joy are still felt, but the important thing is that they do not affect the patient so profoundly. Uncomfortable emotions are more readily and appropriately discharged. Repression with the resultant tension and regression into overt psychotic behavior no longer occurs.

One of the patients was a nurse, 35 years of age, who was a bad alcoholic and an addict to barbiturates and morphine which she used in prodigious quantities. Since her operation she has shown no desire to return to drugs and alcohol.

In spite of these few impressive results, Heath and Pool feel that the operation should not be recommended for any but the most severe neuroses, and then should be carried out only after intensive and skillful psychotherapy has proved valueless.

W. C. A.

HINTS IN DETERMINING IF TARRY STOOLS WERE REALLY DUE TO BLEEDING

Every so often the gastroenterologist is told, perhaps by the physician who is referring a patient, that the man had some tarry stools, and the inference naturally is that he has an ulcer. Sometimes the roentgenologist looks repeatedly and cannot find any sign of an ulcer—what then? There are a number of foods and medicines which are said to produce dark stools, and in all cases of doubt the wise physician will naturally ask if any of these were being taken at the time. A good bit of research for some enterprising young gastroenterologist would be to try out a number of foods to see if any of them really make blackish stools. He might try beets and concord grapes and spinach. Among medicines, the one probably most likely to produce dark stools is bismuth.

Few young physicians today seem to know that there are two or three questions which will usually give a good idea as to whether or not a person's dark stools were due to a hemorrhage from an ulcer. The best question is, "At the time when you had the dark stools, did you get so weak in the knees that you felt like going to bed?" A man with a good-sized hemorrhage from the stomach or duodenum nearly always gets so weak that he prefers to lie down for a few days. One day a physician, on his way to an upper apartment to see a patient, started bleeding and as a result he had to sit down on the stairs; he got too weak to go on up. Sometimes a patient will say "Yes, I went to bed," but on questioning he will admit that he did this solely because his doctor told him to do so. One must always look with doubt on a history of tarry stools if the patient says they did not weaken him.

Another helpful question is, "When you had the tarry stools, did you lose your pain?" As every good gastroenterologist knows, a hemorrhage usually puts a stop to any ulcer pain that may be present. It may even put a stop to headaches or rheumatic pains. Hence, it is that if a man has what are supposed to be tarry stools and continues to have his pain this adds to the suspicion that he did not bleed. Another question is, "Did your doctor, after the episode of dark stools, estimate the hemoglobin, and if so, was it markedly lowered?" If

it was not, there probably was not a hemorrhage. Still another sign of a hemorrhage is marked thirst, a foul taste in the mouth, and marked dryness of the fauces—also for a day or two after a hemorrhage a man is likely to have a slight fever.

W. C. A.

NOTES ON THE NEWER ANALGESIC DRUGS

In a recent article, Dr. Harris Isbell, in charge of research at the hospital for drug addicts maintained by the United States Public Health Service, reported on the use and properties of the newer analgesic drugs. These drugs have been thoroughly tried out in the huge institution at Lexington, Kentucky. The article is in the *Annals of Internal Medicine* for December, 1948.

Dr. Isbell reports particularly on meperidine or demerol, and methadon or amidone. These drugs were discovered in Germany. Another drug used of late is metopon. Interestingly, these new drugs are not chemically related, either to each other or to morphine.

Metopon, in minimal analgesic doses, is less likely to produce sedation and mental dullness than is morphine. There is also less respiratory depression, unless the drug is used with inhalation anesthetics. Then it may produce serious respiratory depression and is, therefore, contraindicated. Metopon is almost as effective in relieving pain when given by mouth as when given hypodermically. Unfortunately, it is hard to manufacture and hence it is about ten times as expensive as morphine.

Meperidine, or demerol, is said to have less respiratory effect than has morphine. It is supposed also to cause less vomiting and nausea, but actual statistics indicate that it may cause more nausea and vomiting than does morphine. According to Batterman, demerol, injected parenterally, causes nausea in 8.4 per cent of cases and vomiting in 3.8 per cent. This would certainly seem to be higher than the incidence of nausea and vomiting with morphine. The comparative figures for nausea and vomiting, given by Lee, were 3.5 per cent and 2.3 per cent.

Demerol appears to relax spasm of the smooth muscle of the gastro-intestinal tract, and also of the ureter. It does not appear ever to increase spasm of smooth muscle as does morphine. Demerol also does not produce constipation, and this is an advantage. It is effective when given by mouth. It is more expensive than morphine and unfortunately it is often unreliable in its action, failing to touch a pain until perhaps it has been given in maximal dosage.

Methadon is similar to morphine in all its pharmacologic actions. It depresses respiration as much as does morphine and causes nausea and vomiting just as frequently. It is also constipating. It is irritating when injected subcutaneously, and if injected repeatedly around one spot it causes severe inflammation

and induration of the skin. Unfortunately, nausea and vomiting almost always occur if the drug is given by mouth.

Patients develop tolerance to all three drugs, but they do this more slowly than with morphine. Metopon is unusual in that tolerance to the analgesic effect is abolished by withdrawing the drug for only eight or fourteen hours. This clearing does not come so rapidly with any of the other drugs.

Unfortunately, there is an abstinence syndrome after the use of all three drugs. Methadon is particularly useful in getting morphine addicts off their habit. All one has to do is shift the man onto methadon and then withdraw that. The symptoms of abstinence are then less intense and less distressing; they come on gradually and they go gradually. The abstinence syndrome with methadon is milder than that produced by the withdrawal of either metopon or meperidine.

Single minimal analgesic doses of methadon and metopon seldom produce significant euphoric reaction in either nonaddicts or former morphine addicts. Single doses of meperidine, however, may produce some euphoria. In large doses, such as addicts use, both metopon and methadon produce a high degree of euphoria.

Evidently, then, all three drugs can produce addiction. All must be used carefully, just as one would use morphine. Unfortunately, many physicians have gotten the idea that demerol is not dangerous, but it is. Many persons have already become addicted to its use. More than twenty such patients have been studied at the hospital in Lexington. Addiction to demerol is more distressing even than addiction to morphine because patients develop tremors, startle responses, and even epileptiform seizures. The moral degeneration is just as bad as with addiction to morphine.

Due to its quick and long-lasting action, its reliability, its powerful sedative action and its relative cheapness, morphine is still the drug of choice for most patients who require relief of pain for a period of less than two weeks. The National Research Council has restricted the use of metopon to persons with some chronic painful disease such as metastatic carcinoma. Demerol has been losing favor because of its lack of reliability and the short duration of its action. Severe grades of pain are often not well controlled with this drug. Methadon is not so good when one wants quick relief from severe pain. It may be good in chronic diseases because the tendency toward habituation is not so marked. For persons who have become addicted to morphine, methadon is the only drug which can satisfactorily be substituted. It is the only one that will suppress all the symptoms of abstinence.

These drugs should never be used for the relief of alcoholism because the alcoholic is so prone to addiction. They should not be used either for the treatment of asthma or migraine because the persons will soon get addicted.

W. C. A.

Book Reviews

AMIALE AUTOCRAT. A Biography of Dr. Oliver Wendell Holmes. *Eleanor M. Tilton*. Henry Schuman. New York, 1947, pp. 470, price \$5.00.

There has long been a need for a good life of Oliver Wendell Holmes, and this book fills the bill. Evidently the author had access to the family letters, and many things can now be said frankly that could not easily be said so long as Oliver Wendell Holmes, Jr. was alive.

The book is decidedly interesting. Because Holmes' life was not very exciting, the main interest comes in the analysis of his unusual character. From boyhood onward he was very talkative, very witty, and full of fun, and much given to making puns. He always wrote easily and well, and early in life he was writing good poetry.

On deciding to take up medicine as a career he studied hard, first in Boston and later in Paris. He was one of that group of able young Americans who brought back from Paris the best of French medicine to the United States. If medical schools had then been more as they are today, Holmes would almost certainly have remained in the laboratory and never practiced. He never seemed to be very fond of practice. From the time of his return to America he was much interested in teaching, and he had his eyes out for a professorship. Eventually this came at Harvard, and he then gave up practice. To eke out a professor's small salary he started lecturing on the Lyceum stages, and soon he became one of the most popular lecturers in the United States. Out of this work came his close connection with the then new *Atlantic Monthly*. For this journal he wrote the immensely popular *Autocrat* and *Professor at the Breakfast Table* series.

As a physician, he doubtless was handicapped by his skill as a writer. Probably his primary interest was in writing and lecturing; but with all this he appears to have been an excellent teacher of anatomy. He worked hard at this job. The students always enjoyed him, and he had a knack of making things clear and interesting. He was the originator of some of those mnemonics which every medical student uses today in memorizing the names of bones.

As a physician, he did one thing that would make any man illustrious, namely, he showed the medical world that puerperal fever was contagious and carried from woman to woman by physicians, and he made the bulk of doctors admit this. Naturally it was a bitter pill for the leading professors of obstetrics, and Hodge and Meigs struck back viciously. A few years later, when Semmelweiss independently made the same discovery, he was so persecuted and hounded that he went insane.

This is another good book for the little shelf that should stand by the side of the doctor's bed. The book-making has been well done, as one would expect from Henry Schuman.

CURRENT THERAPY 1949. *Howard F. Conn, M.D., Editor*. W. B. Saunders Company, Philadelphia and London, 1949, pp. 672.

This is a splendid book which can be of tremendous use to every physician. It

has the great advantage that the many sections on the many different diseases have been written by specialists and recognized leaders in American medicine.

It is a mighty handy book for a doctor to keep within easy reach of his desk chair.

VICTORY IN MY HANDS. *Harold Russell with Victor Rosen.* Creative Age Press, Inc. New York, 1949, pp. 280. Price \$2.50

All those many persons who saw the motion picture *The Best Years of Our Lives* will be the more interested in this unusual story of a soldier who lost both of his hands during the war. It tells of his problems of adjustment to life again, and it tells of the fine work that he has been doing ever since in helping other handicapped soldiers to pick up and carry on.

One of the best things that a physician can do is to read books of this type which show the psychology of patients and particularly their reactions to the good and bad things that physicians do to them.

DIABETES AND ITS TREATMENT. *Joseph H. Barach, M.D.* New York Oxford University Press. 1949. pp. 326

Dr. Barach is Associate Professor of Medicine in the University of Pittsburgh and he has been president of the American Diabetes Association. He is chairman of the Metabolism and Endocrinology Study Section, Research Grants Division, U. S. Public Health Service.

This book was written for the general medical man who wants to treat diabetes more intelligently. Dr. Barach appears to be a good teacher and this book is very attractive. Nearly one-half of the volume is taken up with diets for men, women and children.

Dr. Barach is to be complimented on a splendid job.

HOW PSYCHIATRY HELPS. *Phillip Polatin, M.D. and Ellen C. Phylline.* Harper and Brothers. New York, pp. 242. Price \$3.00.

This is an attractive volume in which the authors explain in simple speech what the various mental illnesses are and what treatments are available. This book offers the inquiring physician some idea of what psychoanalysis is and how it differs from other forms of psychotherapy. It tells if shock treatment is safe and when psychotherapy should be employed. There is a fine list at the end of the authorities in each state who are equipped to give information in regard to psychiatric facilities in the state. So often when a physician and the family of a patient are agreed that he should be under the care of a psychiatrist or perhaps in an institution, the question is where should he go? Naturally the physician who is not doing psychiatry is usually uninformed in regard to these questions.

DISEASES OF THE LIVER, GALLBLADDER AND BILE DUCTS. Second Edition. *S. S. Lichtman, M.D.* Lea and Febiger, Philadelphia, 1949, pp. 1135. Price \$18.00.

This is a splendid book, beautifully written, printed and illustrated, and crammed with information from cover to cover. There are good bibliographies at the close of every chapter. No one who is interested in diseases of the liver can afford to go without this book. Its excellencies are so many that no attempt will be made to single some out for comment.

ABSTRACTS OF CURRENT LITERATURE

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MOUTH AND ESOPHAGUS

JEMERIN, E. E. Results of treatment of perforation of the esophagus. *Ann. Surg.*, 128: 971 (Nov.) 1948.

Prior to 1936, the treatment of 22 patients with perforation of the esophagus (by instrumentation, foreign body or both) was accompanied by 17 deaths, a mortality rate of 77.3 per cent. Only half the group of 22 patients were treated surgically. Since 1936, 90 per cent of a group of 47 patients received surgery. In this group only 8, or 17 per cent, died. Death is from mediastinal infection which follows perforation. The bacteria involved are usually anaerobic, and chemotherapy when used alone has been disappointing. Esophageal perforation should be treated surgically and without delay.

LEMUEL C. MCGEE.

STOMACH

LORENZ, E. AND STEWART, H. L. Tumors of alimentary tract in mice fed carcinogenic hydrocarbons in mineral oil emulsion. *J. Nat. Cancer Inst.*, 9: 173 (Dec.) 1948.

Induction of tumors of the small intestine in the mouse, by feeding olive oil emulsions containing carcinogenic hydrocarbons, has

been reported but carcinoma of the forestomach developed rarely. However, when the emulsions were made acid-stable by the addition of a wetting agent, squamous carcinoma of the forestomach developed frequently. The stabilized emulsion may form a coating on the forestomach permitting intimate and prolonged contact between the carcinogen and the squamous epithelial lining. If this is correct, it follows that any acid-stable, oil-water emulsion containing a carcinogenic hydrocarbon should have a similar effect.

Aqueous mineral-oil emulsions containing methylcholanthrene or dibenzanthracene were given instead of drinking water to four inbred strains of mice (A, C57 brown, dba, I) and strain A backcross hybrids. Squamous cell carcinoma of the forestomach was induced by methylcholanthrene in a large number of mice of strains A and C57 brown and strain A backcross hybrids, but dibenzanthracene induced few such tumors.

Malignant dyskeratosis of the forestomach was induced with methylcholanthrene and dibenzanthracene in animals of all strains but strain I. Like the olive oil emulsions, mineral oil emulsions did not induce any tumors of the glandular stomach. Due to the

cleansing action of the secretions there is probably failure to coat the mucosa with the emulsion. The carcinogen may never actually come in contact with the epithelial cells or the underlying stroma. Gastric adenocarcinoma is readily induced in mice by injection of methylcholanthrene into the walls of the stomach. Few carcinomas and precancerous lesions were induced in the small intestine in contrast with previous experiments in which olive oil emulsions were employed. During and after digestion of the olive oil, the hydrocarbon is precipitated out and thus comes in intimate contact with the intestinal mucosa through which it is absorbed. The mineral oil emulsion does not undergo digestion to any great extent, and the carcinogenic effects on the small intestine and other tissues, as well as the toxic effects, are greatly diminished.

H. NECHELES.

GUISS, L. W. AND STEWART, F. W. Distribution of gastric changes accompanying gastric cancers in various locations. *Arch. Surg.*, 57: 624 (Nov.) 1948.

Following a statistical analysis of the histologic features of a large series of gastric specimens, the authors find that the mean age at which cancer develops in the various areas of the stomach is the same. The average stomach of "normal" persons reaching the cancer age (40 to 79) shows a mild generalized chronic atrophic gastritis with perhaps slight intensification in the pylorus. Gastric cancer, with the exception of cancer of the cardia, is associated with a generalized chronic atrophic gastritis of moderate degree, the gastritis changes being of equal intensity throughout the stomach without regard to the location of the cancer. Although the chronic atrophic gastric changes found in the presence of carcinoma of the cardia might be expected to be more severe in the fundus than in the pylorus, since chronic atrophic gastritis is usually felt to be associated with the presence of carcinoma, the amount actually present is not significantly increased over that found in the "normal" stomachs of persons in the same age group and is definitely less than that found in carcinoma of the body of the stomach. The presence of a duodenal ulcer

has little or no influence on the gastric mucosa. Prepyloric peptic ulcers are associated with a mild atrophic chronic gastritis limited to the pyloric mucosa. The presence of a peptic ulcer in the fundus gland area is associated with a generalized chronic atrophic gastritis of the whole stomach, indistinguishable from that seen in carcinoma of the stomach.

ALBERT CORNELL.

PACK, G. T. AND MCNEER, G. End results in the treatment of cancer of the stomach. Analysis of 795 cases. *Surgery*, 24: 769 (Nov.) 1948.

From 1916 to 1946, 1,200 patients were treated for gastric cancer at Memorial Hospital, N. Y., but follow-up was possible only for the 795 cases occurring between 1916 and 1941. The resectability rate for gastric cancer increased from 2.9 per cent (1916 to 1930) to 39.8 per cent (1942 to 1946). This improvement is due to earlier diagnosis, advances in anesthesiology, and better preoperative and postoperative care. Between 1942 and 1946, the operative mortality for subtotal gastrectomy was 9.8 per cent. From 1916 to 1942, the rate of 5-year survivals was 3.4 per cent, but it has to be considered that in earlier years palliative operations prevailed, and the resectability rate was only 10 per cent. Of patients surviving gastrectomy, 34.7 per cent lived 5 years without recurrence. Duration of symptoms has no bearing on rate of 5-year survivals in this series. Gross pathologic type and microscopic grade of tumors are of prognostic importance. While cancer *in situ* is least dangerous (100% survival, 2 cases), the prospect for annular cancer is most unfavorable (22.7%), probably due to preoperative metastases. Neither the presence of metastases to regional lymph nodes nor penetration of adjacent organs should deter from radical resection. Metastases resulted in considerable lowering of the rate of survival. However, local serosal penetration may sometimes prove a favorable factor, possibly due to the necessity for more radical operation. Gelatinous features in histologic specimens are attended by bad prognosis, even without metastases at time of operation.

L. T. ROSENTHAL.

BOWEL

ROTHENBERG, S., SILVANI, H., CHESTER, S.,
WARMER, H., AND McCORKLE, H. J.

Comparison of the efficacy of therapeutic agents in the treatment of experimentally induced diffuse peritonitis of intestinal origin. *Ann. Surg.*, 128: 1148 (Dec.) 1948.

Fulminating, diffuse peritonitis was produced in 93 dogs by crushing the feces-filled appendix, blocking the blood supply and ligating its base. The spleen and omentum were removed; each animal received 60 cc. of castor oil by gavage. Twenty untreated control animals died of peritonitis with an average survival period of 39 hours. The organisms most often found in the peritoneal fluid were *Clostridia*, *Streptococci* and *Escherichia coli*. Sulfonamide therapy (intravenously, intraperitoneally, or combined) saved no dogs even though the survival period was sometimes prolonged. Intramuscular penicillin, 500,000 units daily, saved each of 5 dogs to whom it was given. The same results were obtained when the penicillin was combined with 2.4 grams of streptomycin given intramuscularly each day. Penicillin-X, 100,000 units given intramuscularly daily, saved 9 out of 10 dogs so treated.

LEMUEL C. MCGEE.

NICKELL, D. F. AND DOCKERTY, M. B. The five year survival rate in cases of completely obstructing annular carcinoma of the descending colon and sigmoid. A pathologic study. *Surg. Gyn. Obs.*, 87: 519 (Nov.) 1948.

A study of the five-year survival rate in 57 cases of completely obstructing annular carcinoma of the descending colon and sigmoid was undertaken by the authors. Factors which contribute to lowered survival rate include damage to the intestinal wall with increased lymphatic absorption, hypertrophy of the musculature, inflammatory swelling and edema, the invasive property of the cancer cell, and the closed-loop type of obstruction of the ileocecal valve. The authors feel that the difference of 26 per cent between the five-year survival rates in obstructing and nonobstructing carcinomas of the descending colon and sigmoid is due to obstruction or the condition of the intes-

tinal wall attending the complication, rather than the size or grade of the lesion.

FRANCIS D. MURPHY.

THOMAS, J. F., DOCKERTY, M. B., AND WAUGH, J. M. Multiple primary carcinomas of the large intestine. *Cancer*, 1: 564 (Nov.) 1948.

During the period, 1907-1944, 132 cases of multiple colonic carcinomas were seen at the Mayo Clinic. This represents 3 per cent of the cases of malignancy of the colon operated upon. The authors emphasize the fact that multiple synchronous and asynchronous carcinomas of the colon are not rare. Multiple lesions are found most frequently in patients with polypi and with a familial history of cancer. Careful manual examination of the colon at the time of operation is necessary so that a second lesion is not overlooked. Postoperatively, all patients who have undergone colonic resections should be examined periodically, since there is an increased possibility of the development of another cancer. Furthermore the return of symptoms need not be considered as necessarily indicative of recurrence or metastases. Certain differences in sex, age, familial incidence and distribution of the lesion, have been observed among the groups of synchronous and asynchronous multiple carcinomas studied.

DAVID A. DREILING.

RAVITCH, M. M. AND McCUNE, R. M., JR. Reduction of intussusception by barium enema. A clinical and experimental study. *Ann. Surg.*, 128: 904 (Nov.) 1948.

Although Hirschsprung, as early as 1876, and Clubbe and Hipsley, a generation later, demonstrated successful reduction of intussusception by enemas, there has been a reluctance on the part of surgeons to use the method as an adjunct to the treatment of this condition.

With dogs in whom intussusceptions have been deliberately produced, the authors have shown that: 1) three feet of hydrostatic pressure within the bowel is tolerated without rupture; 2) intussusceptions readily may be reduced by such pressure within the first 38 hours of the obstruction; and 3) three feet of hydrostatic pressure, furthermore, is unlikely to reduce a gangrenous bowel.

The method, using a barium enema and controlling the hydrostatic pressure, has been applied successfully as the primary treatment in 33 patients. There were no deaths in this group although 9 of these patients required operation to complete the reduction. In 21 solely operative reductions, 5 children died—a mortality of 24 per cent.

The barium technic is described and its use is recommended as an auxiliary to surgery and not in opposition to it.

LEAMUEL C. MCGEE.

REMINGTON, J. H. AND McDONALD, J. R.

Vascular thrombosis in acute appendicitis.

Surgery, 24: 787 (Nov.) 1948.

The authors have studied the origin and frequency of occurrence of vascular thrombosis in acute appendicitis, and have attempted to determine the relationship of this condition to the course of the disease. In a consecutive series of 100 surgically removed appendices, evidence of thrombosis was encountered in 26 instances, involving one or more vessels, and totalling 87 thrombosed vessels. Thrombosis is defined as the presence of fibrin and fibrocytes within a vessel, the walls of which can be definitely identified. In 12 instances, thrombosis occurred only in veins; in 9, only in arteries; whereas in 5 instances, it was encountered in both arteries and veins. In 6 patients, only one vessel was thrombosed and in one instance, as many as 10 vessels; the average was 3.3 vessels. All thrombi appeared in small vessels with a diameter of 100 to 800 microns, most of which located in the submucosa. Gangrene, rupture of the appendix, and fecaliths were more frequent in specimens with thrombosed vessels. The average duration of symptoms in cases with thrombosis was 3 hours longer, and the higher incidence of gangrene and rupture is partly explained through this longer duration of symptoms. It is concluded that thrombosis is secondary to acute appendicitis, depending to a certain degree on the severity of the disease. While thrombosis is generally more frequent among older people, this is not the case in thrombosis associated with acute appendicitis. No relationship existed between the finding of thrombosis in the re-

moved appendix and the postoperative course of the patient.

L. T. ROSENTHAL.

McGraw, J. P., Kremen, A. J., AND RIGLER,

L. G. The roentgen diagnosis of volvulus of the cecum. Surgery, 24: 793 (Nov.) 1948.

Four cases of volvulus of the cecum are reported; in 3, correct roentgen diagnosis was made preoperatively, whereas in 1, the condition was only suspected. Usually part of the terminal ileum and of the ascending colon are also involved, and "volvulus of the right half of the colon" is proposed as a more accurate term. Volvulus occurs in the presence of abnormal mobility of the cecum and ascending colon, and is more frequent in males than in females. Predisposing factors include high residue diet, violent exercise, pregnancy, and tumors. Volvulus of the bowel is produced by torsion of 180 degrees; further twisting would lead to strangulation. There are two clinical types—acute and recurrent. Symptoms are those of mechanical bowel obstruction. Upon physical examination, signs of peritoneal irritation are encountered only after infarction has taken place. Roentgen diagnosis is possible from a simple flat film of the abdomen. Additional evidence will be revealed following barium enema. The diagnosis is based mainly on the following findings: (1) the cecum is dilated and displaced; (2) loops of small bowel, distended with gas, lie to the right of the cecum; (3) appearance of the ileocecal valve at the right of the cecum; and (4) cone-shaped obstruction of the ascending colon upon barium enema. Differential diagnosis of volvulus of the cecum from volvulus of the sigmoid, adynamic ileus, and organic obstruction of the transverse or left colon, is based on roentgenologic and clinical findings.

L. T. ROSENTHAL.

LIVER AND GALL BLADDER

BEGTRUP, H. AND HANSEN, P. F. The re-
action of the liver to small doses of vitamin K as a liver function test. (A diagnostic aid in the differential diagnosis between obstructive and parenchymatous jaundice.) Acta Med. Scand., 132: 29 (Nov.) 1948.

The formation of prothrombin by the administration of vitamin K constitutes the basis for a method recommended as an aid in the differential diagnosis of jaundice. The method is only applicable when there is a reduced prothrombin concentration in the blood.

After an initial determination of plasma prothrombin, 2 mg. of methyl naphthohydroquinonedisuccinate are administered by the oral route. Twenty-four hours later the prothrombin is again measured. The difference between the two values, designated as vitamin K sensitivity, is expressed in percentage; the normal prothrombin level representing 100 per cent. Vitamin K sensitivity in excess of 30, confirmed a diagnosis of obstructive jaundice in 77 per cent of such cases, while a value of less than 30 was encountered in 86 per cent of the cases of parenchymatous jaundice. In the authors' experience, the prothrombin sensitivity test has been more accurate as a diagnostic method than other tests of liver function.

CHARLES A. FLOOD.

TOPP, J. H., LINDERT, M. C. F., AND MURPHY, F. D. Needle biopsy of the liver. *Arch. Int. Med.*, 81: 832 (June) 1948.

Topp and his colleagues have performed 361 biopsies of the liver with the Vim-Silverman needle. There have been no fatalities in their series; four patients showed clinical evidence of hemorrhage; all responded to conservative therapy. In an analysis of the first 111 biopsies, the authors considered 87.4 per cent successful. Among the successful biopsies, 86 per cent were considered to be helpful in the diagnosis. Biopsy is recommended only when the liver is easily palpable. It should be avoided in the region of the gall bladder, in cases of ascites, and in abdominal distention due to ileus.

EDGAR WAYBURN.

COLCOCK, B. P. Carcinoma of the liver—primary and secondary. *Surg. Clinics N. Am.*, 673 (June) 1948.

Primary carcinoma of the liver is described as a rare disease which should be considered in a patient with an irregular, enlarged liver and no evidence of primary cancer elsewhere.

The pathologic types are the hepatoma arising from the parenchymatous liver cells, and the cholangioma arising from the intra-hepatic biliary duct cells. Clinically the disease may be present as the multiple nodular form, with nodules scattered throughout both lobes of the liver, or as a primary malignant tumor which is usually a single large mass with secondary smaller growths surrounding it. The association of the disease with liver flukes suggests that chronic irritation may be a factor in its etiology. Cirrhosis is associated with about 80 per cent of hepatomas and 50 per cent of cholangiomas. The usual symptoms are loss of weight and strength, with anorexia and right upper quadrant or epigastric distress. There may be a palpable mass and secondary anemia. The only hope of treatment is resection of the lesions where they are single.

Secondary carcinoma of the liver may appear very similar to benign tumors (fibromas, cysts, scirrhous angiomas) at operation. The liver involvement in direct extension from the cancer of the stomach is often not as great as it appears and in many instances the invasion is really only an adhesion to Glisson's capsule. Solitary metastases secondary to carcinoma of the rectum and colon should be removed in most cases.

FRANK G. VAL DEZ.

WILKINSON, S. A. The value of duodenal drainage: its place in diagnosis. *Surg. Clinics N. Am.*, 587 (June) 1948.

The indications for this procedure in diagnosis are listed as: 1) gall bladder disease where the Graham-Cole Test is doubtful, 2) suspicion of a common duct stone especially where the gall bladder has previously been removed, 3) verification of the diagnosis of cholangitis, 4) obstructive jaundice, and 5) suspected malignancy. The contraindications are: 1) a diagnosis satisfactorily established by other procedures, 2) patient too weak to undergo the procedure, and 3) case where surgery will be done regardless of the information obtained.

The method of duodenal drainage is described. The gross examination should include observation of color, clarity, turbidity, amount of precipitate, and presence

of gross blood and bile in the specimen. The microscopic examination of the specimen should include looking for bile-stained pus cells with an estimate of their quantity, bile-stained columnar epithelial cells, bile-stained bacteria, calcium bilirubinate crystals and cholesterol crystals. With regard to interpretation of findings, it is stated that clumps of bile-stained pus cells and bacteria often appear in acute and chronic hepatitis; bile-stained columnar epithelial cells usually indicate disease or infection of the biliary tree; gross blood indicates malignancy; cholesterol crystals and calcium bilirubinate pigment indicate stones.

One thousand cases are reviewed of which, 531 were normal, 236 showed evidence of biliary tract infection, 237 suggested common duct stone and 6 suggested malignancy. Of the cases subsequently operated, this diagnostic procedure was found to be 94 per cent accurate.

FRANK G. VAL DEZ.

SWINTON, N. W. AND BECKER, W. F. Tumors of the gallbladder. *Surg. Clinics N. Am.*, 669 (June) 1948.

Benign tumors of the gall bladder are very rare. They are occasionally discovered by X-ray. The authors advise cholecystectomy when they are found.

Malignant tumors of the gall bladder are discussed with regard to incidence, relation to cholelithiasis, symptoms, histologic picture, treatment and end results. A fair estimate of its incidence is five per cent of all malignancies. It is most common in the 50-70-year age group and it is four times as frequent in females than in males. Four to five per cent of cholelithiasis cases are associated with malignancy of the gall bladder, and 76 to 87 per cent of the gall bladder malignancies have gall stones present. The authors believe that all cases of cholelithiasis should have a cholecystectomy if there are no contraindications. There are no early symptoms of gall bladder malignancy, the first symptoms usually being those of cholelithiasis. Jaundice may be present and is persistent and progressive. A mass, weight-loss and acholic stools may be evident.

Histologically, malignancy of the gall

bladder is divided into adenocarcinoma, alveolar carcinoma, and squamous cell carcinoma. There is usually early invasion of the gall bladder wall with extension to the lymph nodes and liver. The lesion may also extend downward into the common duct. The treatment is surgical, the procedure depending upon the extent of the lesion. The prognosis is poor, a 5-year survival being achieved in no more than 6 per cent of patients.

FRANK G. VAL DEZ.

WILKINSON, S. A. The differential diagnosis of jaundice. *Surg. Clinics N. Am.*, 575 (June) 1948.

The various types of jaundice are considered and methods for differentiating them are described. Retention jaundice is discussed as including hemolytic jaundice, and jaundice due to minor degrees of subnormal liver function. Regurgitation jaundice may be due to diseases in which the liver cells are badly damaged and much of the sodium bilirubinate leaks into the lymph spaces and central vein, or it may be secondary to extra-hepatic obstruction with secondary damage to the liver cells, or it may be due to a cholangitis where the bile escapes into the blood through the dilated bile capillaries.

Various laboratory tests are recommended as aids in the differential diagnosis. The serum bilirubin is important; the direct reaction measuring the sodium bilirubinate and the total reaction measuring the sodium bilirubinate plus the bilirubin globin. Therefore in uncomplicated cases, the direct reaction will be low in retention jaundice and high in obstructive jaundice. The brom-sulfalein test will give high values in all cases except those of hemolytic and mild retention jaundice. Urobilinogen determinations are also important; these levels will be increased in the feces with hemolytic jaundice, increased in the urine with liver damage, and absent from both feces and urine in obstructive jaundice. The serum colloid and electrolyte tests are described as being the most sensitive of the liver function tests and determination of serum cholesterol and cholesterol esters is sometimes of definite value.

FRANK G. VAL DEZ.

MARSHALL, S. F. AND PHILLIPS, E. S. The acute gallbladder. *Surg. Clinics N. Am.*, 633 (June) 1948.

In the treatment of acute cholecystitis the authors classify as early surgery, that done within the first 72 hours after the onset of symptoms; intermediate surgery being performed later than 72 hours but before the cessation of symptoms, and late surgery being done after a clinical remission of the attack. A series of 74 pathologically-proven cases of acute gall bladder disease is reported. Of these, 11 were operated within the first 72 hours and the remaining 63 from 4-7 days after the onset of symptoms. There was one postoperative death giving a mortality rate of 1.3 per cent.

The authors believe that early surgery is the treatment of choice because of the lesser inflammation in this period and because the serious complicating factors may be prevented. Since there is a high incidence of common duct stones in these cases, they should be sought for and removed when present. Choledochostomy may be indicated particularly in elderly patients or those who are in poor condition. It is suggested that early operation will reduce the mortality in the older age group because it lessens the hazards of depleted reserves in cases of concomitant diseases.

FRANK G. VAL DEZ.

KIEFER, E. D. The diagnosis and treatment of portal cirrhosis of the liver. *Surg. Clinics N. Am.*, 713 (June) 1948.

With regard to symptomatology of portal cirrhosis, it is stated that the early symptoms are nonspecific; symptoms of portal hypertension appear in the more advanced cases; and symptoms of hepatic insufficiency appear in the far advanced cases. Physical examination may reveal an enlarged or a small and irregular liver. Compensation for portal obstruction may be evidenced by dilated abdominal veins, hemorrhoids, and spider angiomas. Ascites is often present in moderately advanced cases and dependent edema may appear with marked liver damage. Jaundice is usually not marked. Laboratory examination may reveal elevated serum bilirubin. Liver function tests may reveal hepatic insufficiency. A large percent-

age of esophageal varices can be demonstrated by X-ray. Liver biopsy may be done but the complication of hemorrhage should be borne in mind.

The most important points with regard to treatment in the early cases, are cessation of alcohol, adequate nourishment and bed rest. When hepatic insufficiency exists, a high-carbohydrate, high-protein, low-fat diet, and large doses of vitamins and lipotropic substances are in order. Ascites may be treated surgically by the insertion of a button to maintain a sinus between the peritoneum and subcutaneous tissue. Medical measures such as salt restriction and mercurials may help. Lowered serum protein is treated with whole blood, plasma and serum albumin. Gastrointestinal hemorrhage should be treated with complete rest, sedation, and transfusion. Some cases of bleeding esophageal varices have been controlled by the insertion and inflation of a latex bag. Injection of the varices with sclerosing agents may be performed. Portal hypertension may be treated with anastomoses between the portal and systemic venous circulations but this is a hazardous procedure in portal cirrhosis.

FRANK G. VAL DEZ.

KINSELL, L. A., MICHAELS, G. D., BARTON, H. C., AND WEISS, H. A. Protein balance studies in patients with liver damage. II—The role of lipotropic agents. *Ann. Int. Med.* 29: 881 (Nov.) 1948.

It is the object of this paper to evaluate the role of methionine or choline, alone or combined, in the treatment of acute and chronic liver disease. In an earlier paper, the authors concluded that patients with liver disease tend to show a negative nitrogen balance, or major qualitative disturbances in protein formation. It is assumed that improved protein anabolism will be beneficial in the treatment of liver disease. Six patients with acute hepatitis were studied. However, on account of the rapidly changing nature of the disease, no definitive evaluation was possible. No conclusions could be drawn as to the beneficial effect of choline or methionine in acute liver disease. In one patient with chronic active hepatitis, a catabolic effect was obtained. Five patients with chronic active

liver disease, placed on a high vitamin, high protein intake, were studied as to the effect of choline and methionine on their nitrogen balance. Choline chloride (9 gm. daily) produced a profound anabolic effect in patients with a sufficient amount of salvageable liver tissue. This action may not take place on a lipotropic basis, as one of the patients studied failed to show any excess hepatic fat deposition. No additional anabolic effect was obtained through administration of methionine (dl-methionine, 8 gms. daily). All nitrogen balance studies were designed to demonstrate this "non-choline" effect of methionine. No definitive conclusions are drawn as to the value of yeast, alpha tocopherol, or parenteral liver extract. However, the possible deleterious effect of liver extract is discussed.

L. T. ROSENTHAL.

COMFORT, M. W., GRAY, H. K., AND WILSON, J. M. The silent gallstone: A ten to twenty year follow-up study of 112 cases. *Ann. Surg.*, 128: 931 (Nov.) 1948.

This study is based on information obtained by follow-up letters sent to patients who are known to have had gallstones as an incidental finding at the time of abdominal surgery undergone 10 to 20 years before receiving the letter of inquiry. One hundred and twelve replies were received from patients whose laparotomies were *not* brought about because of abdominal cancer, peptic ulcer, colic, indigestion, or other symptoms which conceivably may have been due to the gallstones.

Twenty-one patients reported colic as a subsequent development and more than half of these had had repeated attacks. Five had both colic and jaundice. Thirty additional patients in the group of 112 had "indigestion" (abdominal discomfort, intolerance to certain foods, heartburn, etc.) without colic. Therefore, less than half of the group had symptoms which may be attributable to the presence of gallstones during the one or two decades. Cholecystectomy had been performed in 24 of the 51 cases with symptoms. Three of these died postoperatively. Twenty-eight of the 112 patients had died of miscellaneous causes unrelated to their

calculi. Six had died of cancer, not one of which had cancer of the gallbladder.

What should be the physician's attitude toward the patient with a "silent" gallstone? From this experience such a patient may be told "that he has about an even chance that symptoms will develop, that he has about one chance out of five that painful seizures will develop and a small chance that jaundice will develop within 10 to 20 years. . . . Cholecystectomy may be advised but need not be urged, if the patient prefers to accept the chance of experiencing painful seizures or the increased risk of surgical treatment in the event the complication of calculus disease of the biliary tract appears."

LEMUEL C. MCGEE.

PANCREAS

LIUM, R. AND MADDOCK, S. Etiology of acute pancreatitis. An experimental study. *Surgery*, 24: 593 (Oct.) 1948.

The theory of retrograde bile flow into the pancreatic ducts producing acute pancreatitis is not tenable. Rather it would appear that this disease occurs when there is sudden obstruction of the outlets of the pancreas in an actively secreting gland. The obstruction may be due to mechanical factors, edema and spasm of the sphincter of Oddi, or from edema and hyperemia of the duodenal mucosa secondary to an irritant such as alcohol. The pancreatic juice ruptures the ducts and initiates the inflammatory reaction. If the pressure and enzymatic concentration are not great, the process may end at this stage with only a mild degree of pancreatitis. Should either factor persist, the process proceeds from mild inflammatory changes within the septa to dissolution of the entire lobule and inflammatory replacement. The damage is commensurate with the volume and enzyme content of the extruded secretion.

Experimental evidence supporting this theory was obtained by studies using cats. The pancreatic ducts were carefully tied and various stimulants were given. Twenty-four to forty-eight hours later, sections were taken from the tail of the pancreas. No fat necrosis occurred in the controls. Starved animals stimulated with pilocarpine, acetylcholine and eserine had minimal fat necrosis.

Secretin-stimulated animals, and those in which the ducts were tied after feeding, showed diffuse inflammation with scattered areas of marked damage. The most constant and extensive changes were in the group stimulated by feeding.

MARCEL PATTERSON.

MOUSSEAU, L. P. AND KLING, S. Pancreatic pseudocyst. *Can. Med. Assoc. J.*, 59: 550 (Dec.) 1948.

The author states that only 53 new cases of pancreatic pseudocyst have been reported in the last decade. The cyst forms as a result of destruction of an intermediate portion of the pancreas and its ducts by inflammation, trauma or vascular disturbance, leaving a severed portion of pancreas unconnected with the digestive system. Treatment consists in complete removal of that distal portion of the pancreas forming the cyst. A pseudocyst was found in a 37-year old male who, 2 years previously, had had an acute pancreatitis with necrosis, both diagnoses having been confirmed by laparotomy and tissue biopsy. The symptoms consisted of episodes of epigastric pain, flatulence and vomiting. An almost complete excision was performed and the abdomen closed without drainage. The patient recovered completely. Although practically no pancreas remained, he has not manifested a diabetic tendency.

JOSEPH B. KIRSNER.

THOMAS, J. E. The functional innervation of the pancreas. *Rev. Gastroenterol.*, 15: 813 (Nov.) 1948.

Stimulation of the vagus nerve appears to increase the external secretion of the pancreas both in volume and in enzyme concentration, particularly the latter. Other effects include increases in the pancreatic blood supply and in the secretion already induced by secretin. Inhibitory fibers to the pancreas have also been demonstrated in the vagus. The splanchnic nerves have been shown to carry fibers similar in function to those found in the vagus. Cutting the extrinsic nerves to the pancreas has surprisingly little effect on its function; in the case of the vagus, the cephalic phase of secretion is lost, but the stimulating effect of meals on the enzyme output is still present though less than

normal. In contrast, paralytic doses of atropine profoundly depress secretion of enzymes in response to all types of alimentary stimuli. This suggests that there is more to the innervation of the pancreas than is comprised in the vagus and splanchnic fibers, but this additional mechanism has not been established.

C. WILMER WIRTS, JR.

ANEMIAS

HALL, B. E. AND CAMPBELL, D. C. Vitamin B₁₂ therapy in pernicious anemia. I. Effect on hematopoietic system: Preliminary report. *Proc. Staff Meet. Mayo Clinic*, 23: 584 (Dec.) 1948.

A crystalline compound isolated from liver was shown by Shorb to be highly active in promoting growth of *Lactobacillus lactis* Dorner; this compound has been designated as vitamin B₁₂. West demonstrated that small quantities of this new substance induced a marked hematopoietic response in cases of pernicious anemia in relapse. Vitamin B₁₂ was administered to 11 patients, eight of whom had never had previous anti-anemic therapy. Eight of the patients had initial red counts of less than two million red blood cells per ccm. Within 4-7 days after beginning therapy, reticulocyte responses of 7.2 to 39.0 per cent were noted. Values for leukocytes and blood platelets returned to normal in all patients who had subnormal counts prior to the institution of therapy. It has been found that 1.0 microgram of vitamin B₁₂ has approximately the same hematopoietic effect as 1 U.S.P. unit of liver extract. Sternal puncture aspirations revealed restoration to normoblastic marrow which was virtually complete in 48 hours in patients given relatively large doses of vitamin B₁₂.

FRANK NEUWELT.

HALL, B. E. AND CAMPBELL, D. C. Vitamin B₁₂ therapy in pernicious anemia. II. Effect on the general clinical and neurologic manifestations: Preliminary report. *Proc. Staff Meet. Mayo Clinic*, 23: 591 (Dec.) 1948.

All 11 patients, aside from the severe primary anemia, had the usual symptoms found associated with pernicious anemia: 6 had glos-

itis, 3 had peripheral neuritis, and 6 had peripheral neuritis as well as early or moderately advanced subacute combined cord degeneration. The results of parenteral therapy with vitamin B₁₂ on these associated symptoms are similar to those found after treatment with liver extract or gastric mucosal extracts. Gastrointestinal symptoms, including glossitis and burning or soreness of the mouth, are relieved quickly—long before complete regeneration of the lingual papillae. Varying degrees of improvement were found in the neurologic conditions, both in the peripheral neuritis and the subacute combined cord degeneration. In 3 of the 6 patients with combined degeneration, the degree of improvement was marked. Improvement in strength, gain in weight, better appetite and mental alertness were noted. These patients were studied for periods of from 1 to 5 months following the institution of vitamin B₁₂ therapy.

FRANK NEUWELT.

MARTIN, J. D., JR., ROBERTSON, R. L., AND DENNIS, E. W. Anemia following resection of intestine. Clinical and experimental observations. *Surgery*, 24: 819 (Nov.) 1948.

Anemia following gastrectomy and resection of the intestine appears most commonly as normochromic normocytic anemia. Next in frequency is hypochromic anemia developing from nutritional deficiencies; it responds well to administration of iron, vitamins, and foods, and to elimination of infection. Two cases are reported in which hyperchromic macrocytic anemia developed following extensive resection of the intestines. The condition failed to respond to iron medication, but administration of folic acid (25 mg. daily) was followed by reticulocyte response and eventual return of erythrocyte count and hemoglobin to normal levels. Three earlier instances of hyperchromic macrocytic anemia, developing after resection of the small intestine and combined either with hypochylia or achylia, are reported in the literature. Castle had shown that interaction between an "extrinsic" factor ingested in the diet, and an "intrinsic" factor in the gastric secretions, occurs in the production of red blood cells. In order to eliminate the

intrinsic factor, Petri resected parts of the small intestine of puppies, and produced hyperchromic macrocytic anemia about 2 months postoperatively. In experiments of the authors, extensive resection of the small intestine of 12 adult dogs failed to produce hyperchromic macrocytic anemia, as observed in patients following similar operative procedures. Resulting anemia proved not constant as to type, and did not respond to folic acid. Postoperative hyperchromic macrocytic anemia may be due to faulty absorption of factors which in normal individuals prevent the occurrence of macrocytosis.

L. T. ROSENTHAL.

ULCER

LEWISON, E. F. The treatment of bleeding peptic ulcer. *Southern Med. J.*, 41: 1031 (Nov.) 1948.

A statistical report, describing the treatment of 218 cases of bleeding peptic ulcer seen at Johns Hopkins Hospital from 1928 to date, is given. The group of patients treated by starvation had a mortality of 54 per cent, whereas, in the group on the Meulengracht diet, there was no mortality. Of the 136 patients treated medically, 12 (8.8%) died, while of the 82 patients who were operated upon after the hemorrhage had stopped or at least "decreased in tempo", 4 (4.9%) died. Seven patients were subjected to vagotomy, and, six months later, there had been no recurrent bleeding.

ANTHONY M. KASICH.

PAULSON, M. AND GLADSDEN, E. S. Medical management following vagotomy for peptic ulcer. *Med. Clinics N. Am.*, 1711 (Nov.) 1948.

This paper is based on two years' experience with 50 patients subjected to vagotomy, with or without gastroenterostomy or subtotal gastric resection. Following vagotomy alone, X-ray studies demonstrated gastric dilatation, decreased peristalsis, and delayed gastric motility. Vagotomy produced but little influence on other viscera. Some transient dilatation of the upper jejunum was noted. The advantages of vagotomy with regard to alleviation of pain, heartburn, and the patient's general condition are empha-

sized. No recurrent ulcerations were observed subsequent to vagotomy. Postoperative complications, (e.g. chest pain following the transthoracic approach, and diarrhea) were of short duration. However, epigastric fullness and foul regurgitation proved annoying in some instances. The "dumping" as well as the "hypoglycemic" syndromes occur following associated anastomosis. The differential diagnosis between the dumping and hypoglycemic syndromes is based on the fact that they occur at different intervals following meals.

Patients with vagotomy, alone or combined with gastroenterostomy, received unrestricted diet. Six smooth feedings are prescribed to patients with associated subtotal resection; this schedule may subsequently be liberalized. Fullness, nausea, vomiting, and regurgitation as after-effects of simple vagotomy were treated with urecholine (Merck). In two instances in which urecholine was unavailable, gastric retention made reoperation necessary. The dumping syndrome is treated by elimination of bulky food which leaves the stomach rapidly, and causes dilatation of the jejunum. Hypoglycemia is prevented through a routine of frequent feedings, thus supplying carbohydrates when needed. Fruit juices are given for the immediate relief of symptoms.

L. T. ROSENTHAL.

WEISS, J. Treatment of gastric and duodenal ulcers with anion exchange resins. *Rev. Gastroenterol.*, 15: 826 (Nov.) 1948.

Forty-four patients, with duodenal and gastric ulcers proven by X-ray, were treated with an anion exchange resin. Forty patients had symptomatic relief in 1-8 days, whereas 3 with gastric ulcers and 1 with malignancy had no response. The average time of X-ray regression of the ulcer crater, in the 39 successful cases, was 10 to 14 days. The resin had no apparent effect on the bowels; it produced neither diarrhea nor constipation.

C. WILMER WIRTS, JR.

CASH, S. L. AND MARSHALL, F. A. Chronic benign gastric ulcer on the greater curvature. *Rev. Gastroenterol.*, 15: 821 (Nov.) 1948.

Two cases demonstrating benign chronic

ulceration on the greater curvature of the stomach are reported; only one came to surgery. The authors quote Blum, who, on the basis of histological section and limitation to exactly the greater curvature line, found only sixteen proven cases of benign ulcer reported.

C. WILMER WIRTS, JR.

SHAY, H., GRUENSTEIN, M., SIPLET, H., AND KOMAROV, S. A. Protection of gastric mucosa of the rat against ulceration by prefeeding with protein hydrolysates. *Proc. Soc. Exp. Biol. Med.*, 69: 369 (Nov.) 1948.

Experiments were done to analyze the cause of beneficial effects, which Co Tui and others report to result from addition of protein hydrolysates to the diet of patients with ulcers. The method of assay involved the use of the Shay rat. An adequate diet, with protein hydrolysates added in amounts equivalent to 25 per cent of additional protein, produced a marked increase, in rats, in the resistance of the gastric rumen to peptic ulceration without concurrent changes in volume, acidity, or peptic power of the gastric contents.

H. NECHELES.

SURGERY

CLAGETT, O. T. AND WAUGH, J. M. Indications for and advantages of Schoemaker-Billroth I gastric resection. *Arch. Surg.*, 56: 758 (June) 1948.

In the past 5 years, the Schoemaker-Billroth I type of gastric resection was done in 183 cases. Many of these operations were performed for lesions of the stomach which did not involve the duodenum. Patients who have undergone this type of operation have less trouble with digestion, intestinal motility and nutrition than do patients who have undergone any other type of gastric resection. With the Polya type of resection, patients are more likely to have digestive disturbances, such as the "dumping syndrome." Other advantages of the Billroth I type of resection are as follows: 1) It is the quickest and easiest type of partial gastric resection that can be performed. 2) It avoids the additional steps of duodenal closure and disturbance of the colon and mesocolon necessary in the more commonly performed

gastric resections. 3) It accomplishes the objectives of gastric resection with a minimum of surgical trauma and handling of tissue. 4) It is a safe operation when used according to the indications mentioned. 5) It is a physiologic operation because it restores normal gastroduodenal continuity. The chief contraindications to the use of the Billroth I resection for lesions requiring gastric resection involve the duodenum. Fixation, shortening, narrowing or induration of the duodenum will prevent the establishment of a safe and satisfactory anastomosis. In most other circumstances, this type of operation provides a means of gastric resection that offers many advantages over the more commonly performed types of gastric resection.

ALBERT CORNELL.

KREMEN, A. J. A combined abdominothoracic incision particularly adapted for use in total gastrectomy and esophagogastricectomy. *Surgery*, 24: 605 (Oct.) 1948.

A surgical approach, especially useful for high gastric lesions with involvement of the lower esophagus, is described. It was also used successfully in one case of paraesophageal hernia. With the patient in a supine position and the left side elevated to ten degrees, a skin incision is made from the lateral edge of the right rectus muscle slightly above the umbilicus and extended horizontally and upward to the left costal margin where the eighth costal cartilage crosses the seventh interspace. The abdominal portion of the incision is then carried through into the peritoneal cavity allowing exploration. If decision is made for resection, the operating table is rotated, elevating the left side of the patient to about twenty-five degrees. The eighth costal cartilage is removed and the excision extended into the pleural cavity. The left phrenic nerve is crushed and the diaphragm is incised. The extent of the diaphragmatic incision depends upon the amount of esophagus to be resected.

The advantage of the incision is that the added exposure allows for more careful dissection, preparation, and anastomosis with less likelihood of leakage and infection. The disadvantages are that, without the lateral rotation of the patient, the heart will inter-

fere with exposure, and the dissection of the esophagus is limited to below the hilus of the lung and the inferior pulmonary vein.

The technique for closure is given. Ten patients are described in which the incision was used. There were no complications attributable to the incision.

MARCEL PATTERSON.

BLACK, B. M. Combined abdomino-endorectal resection. A surgical procedure preserving continuity of the bowel, for the management of certain types of carcinoma of the midrectum and upper part of the rectum. *Proc. Staff Meet. Mayo Clinic*, 23: 545 (Nov.) 1948.

A brief resume of various operations to preserve the anal sphincter is given, pointing out that most such operative procedures have been rather unsatisfactory. Babcock reintroduced the principle of the preservation of the sphincter in this country in 1932 and further work on this problem stems from his efforts. The author's combined abdomino-endorectal resection results in a more satisfactory type of sphincter control. He emphasizes that an intact anal canal must be present in order to have normal control. Therefore, in the present operation, the rectum is divided 2-3 cm. above the dentate margin. The precise technique for resecting the involved segment of bowel is explained; it includes constructing a new pelvic floor whenever possible. The endorectal phase of the operation is carried out with the patient in a lithotomy position. The bowel is pulled through the dilated rectum, by means of a hemostat, to a point beyond the lesion at which the normal bowel is anchored to the perineal skin. The diseased portion of bowel is then severed. The protruding sigmoid is opened after several days. After several weeks, the redundant sigmoid is amputated above the level of the sphincter but below the union of sigmoid and anal canal, which union is quite firm by this time. Seven such operations have been performed without mortality and with excellent results in 4; in 2 others, the unsatisfactory degree of continence may be due to lack of confidence rather than poor sphincter tone and control.

FRANK NEUWELT.

SPAK, I. "Palliative gastrectomy" in cases of duodenal ulcer. *Acta Chir. Scand.*, 97: 91 (Nov.) 1948.

In 41% of the author's series (98 cases), a palliative gastrectomy was performed, i.e. a partial gastrectomy with or without removal of the pylorus and without resection of the duodenal ulcer. This operation was done in those cases in which the ulcer so distorted the duodenum or was so located, that adequate closure was difficult or impossible and the danger of injury to the common duct was great. The author believes the pylorus can be left *in situ* and is not a factor in the production of stomal ulcer or in the healing of the duodenal ulcer. He cites a collected series of 2,000 cases of duodenal ulcer in which palliative resections were done in 1,415, with a postoperative stomal ulcer incidence varying from 1.8-5.5 per cent. Also reported are 98 cases in which a prepyloric ausschaltung with retrocolic Billroth II gastroenterostomy was done. There were 2 deaths (2%). Of the 83 cases with adequate follow-ups, averaging 4.4 years, 91.6 per cent of the results were satisfactory; 17 per cent had free acid. There were no marginal ulcers.

DAVID A. DREILING.

PATHOLOGY

POPPER, H. AND FRANKLIN, M. Viral versus toxic hepatic necrosis. *Arch. Path.*, 46: 338 (Oct.) 1948.

A group of 154 cases of viral and toxic hepatitis are presented with careful analysis of the macroscopic and microscopic differences between these two forms of liver disease. The viral form, which spreads irregularly throughout the liver, results in the sudden death of cells and is associated with a mesenchymal reaction of mononuclear phagocytizing cells. In the toxic form, zonal arrangement is more prominent, the death of cells more gradual, and the inflammatory reaction is milder and polymorphonuclear in type. The liver is larger in the toxic form and renal damage more prominent. The clinical manifestations of the two forms are interpreted in the light of speed and mechanism of development of the liver injury.

DAVID A. DREILING.

GUISS, L. W. AND STEWART, F. W. Histo-

logical basis for anacidity in gastric disease. *Arch. Surg.*, 57: 618 (Nov.) 1948.

This study was based on 32 stomachs resected for duodenal ulcer, 19 stomachs with prepyloric ulcers, 20 stomachs resected for peptic ulcer of the body of the stomach, 92 gastric specimens resected for carcinoma arising in the pyloric gland area and 113 stomachs with carcinoma involving the fundus gland area. Considerable variation in the appearance of the parietal cells was observed. The number of normal-appearing parietal cells in the mucosa of the gastric fundus is directly dependent on the degree of chronic atrophic gastritis present. Increases in the intensity of the gastritis result in a proportionate decrease in the number of parietal cells. The production of free hydrochloric acid and the figure obtained for free hydrochloric acid on gastric analysis are directly proportional to the number of normal-appearing parietal cells present in the fundus mucosa. The degenerative changes of chronic atrophic gastritis are the basic cause of hypoacidity and anacidity in gastric disease. It is unnecessary to postulate the influence of a gastric secretion inhibitory factor to explain the hypoacidity and anacidity associated with gastric carcinoma. The variations in secretion of the hydrochloric acid correspond to proportionate variations in the number of normal-appearing parietal cells present in the fundus mucosa. The high figures for free hydrochloric acid obtained in cases of duodenal and prepyloric peptic ulcer are due to the relative freedom of the fundus from gastritic changes. The figures for free hydrochloric acid, obtained by gastric analysis properly done, may be considered a valuable index to the degree of degenerative gastritic change present in the fundus of the stomach.

ALBERT CORNELL.

MOORE, C. E., STATE, D., HEBBEL, R., AND TRELOAR, A. E. Carcinoma of the stomach. The validity of basing prognosis upon Borrmann typing or the presence of metastases. *Surg. Gyn. Obs.*, 87: 513 (Nov.) 1948.

An analysis of the prognosis of carcinoma of the stomach based upon Borrmann typing or the presence of metastases is presented.

It is felt, by the authors, that the presence or absence of demonstrable metastases in regional nodes, in patients subject to gastric resection, has a greater prognostic value than the Borrmann type of tumor. However, the Borrmann type provides a proportionately large number of patients free of metastases in the cases of limited tumors, while the infiltrating tumors are more likely to metastasize.

The authors conclude that metastases cannot be accurately determined preoperatively and that patients should not be denied operation because of the type tumor determined.

FRANCIS D. MURPHY.

PHYSIOLOGY: SECRETION

SIPLET, H. KOMAROV, S. A., AND SHAY, H. The estimation of mucin in gastric juice. *J. Biol. Chem.*, 176: 545 (Nov.) 1948.

The authors have found that a modification of Tollens' naphthoresorcinol reaction for glucuronic acid, with the use of a photoelectric colorimeter, was a reliable method of estimating the concentration of mucin in gastric juice. The work was based on 2,800 determinations over a period of two years; gastric juices were obtained from dogs with a gastric fistula.

Preliminary experiments indicated that true recoveries of glucuronic acid could be expected if the solutions were boiled for four hours and there was some preliminary hydrolysis preceding the coupling with naphthoresorcinol. Later experiments indicated that separate hydrolysis was not reliable because of deterioration of the standards and that the best procedure was the 30, 60, and 240-minute, simultaneous procedure. In experiments with protein precipitates, it was concluded that the glucuronic acid of gastric juice was derived almost exclusively from its protein constituents. Observations on mucin content of gastric secretions under different conditions of stimulation were discussed briefly with the conclusions that the lowest concentrations were found following histamine, the highest in the alkaline mucus of a fasting stomach, and intermediate values after sham feeding.

FRANCIS D. MURPHY.

MIRSKY, I. A., BLOCK, S., OSHER, S., BROH-KAHN, R. H. Uropepsin excretion by man. I. The source, properties and assay of uropepsin. *J. Clin. Invest.*, 27: 818 (Nov.) 1948.

The presence in the urine of an enzyme, uropepsin, with proteolytic activity at strongly acid reactions, has previously been demonstrated but methods of its study have often been inaccurate, and processing the urine has been a long and laborious task. By using a method, in which urine requires only ten minutes' incubation, and which yields accurate results, experimentation by these authors has been greatly facilitated. It is proposed that the study of uropepsin activity in the urine may obviate the inconvenient and time-consuming methods of gastric analysis now in general use.

It has already been shown that uropepsin is not found in the urine of gastrectomized dogs or cats, or patients with the achylia gastrica of pernicious anemia, and it may therefore be concluded that uropepsin undoubtedly originates as the result of the peptic activity of the gastric mucosa. The peptic glands of the stomach secrete a proenzyme, pepsinogen, which undergoes autocatalytic conversion to active pepsin in the presence of the hydrochloric acid in the lumen of the stomach. It is felt that uropepsin is derived from the direct secretion of pepsinogen into the blood stream by the secreting glands themselves, and not from the reabsorption of pepsin from the lumen of the stomach. Gastric secretory activity is essential for the formation of uropepsin. The proteolytic activity of the urine at acid reactions can probably be ascribed primarily to the activity of uropepsin.

SAM OVERSTREET.

BROH-KAHN, R. H., PODORE, C. J. AND MIRSKY, I. A. Uropepsin excretion by man. II. Uropepsin excretion by healthy men. *J. Clin. Invest.*, 27: 825 (Nov.) 1948. Twenty-seven apparently healthy men were used for the further investigation of the nature and activity of uropepsin, and to define the factors regulating its excretion. It is learned that uropepsin is excreted at a fairly constant rate by the healthy adult male. While the ingestion of food influences

the secretion of gastric juice, it seems to play no significant role in the regulation of uropepsin excretion. Healthy men excrete appreciable quantities of uropepsin at a fairly constant rate throughout the day, and from day to day. The rate is not markedly affected by volume, specific gravity or acidity of the urine, or by wakefulness, sleeping or ordinary exercise of the subject. The rate of uropepsin excretion is characteristic of the individual. Its excretion seems to be a function of the endocrine rather than the exocrine activity of the peptic glands of the stomach.

SAM OVERSTREET.

PODORE, C. J., BROH-KAHN, R. H., AND MIRSKY, I. A. Uropepsin excretion by man. III. Uropepsin excretion by patients with peptic ulcer and other lesions of the stomach. *J. Clin. Invest.*, 27: 834 (Nov.) 1948.

Uropepsin assays were performed on 695 night specimens of urine from 30 patients with benign gastric or duodenal ulcers, and it was revealed that the mean excretion was approximately twice that obtained in normal healthy men. A total of 72 assays were performed on 9 patients with pernicious anemia and in no case was uropepsin detected. These results confirm the conclusions previously formed by other workers. In a total of 247 assays from 14 subjects, who presented gastric complaints but no demonstrable peptic ulcer or other organic lesion, the uropepsin excretion rates were definitely lower than in those having peptic ulcer. From these observations, it may be expected that uropepsin assays may become a useful adjunct in the diagnosis of peptic ulcer. It is believed that there is no causal relationship between gastric hyperacidity and uropepsin excretion.

SAM OVERSTREET

PHYSIOLOGY: MOTILITY

KEEFER, G. P. Small intestinal motility in acute dysentery. *Am. J. Roent. Rad. Therapy*, 60: 587 (Nov.) 1948.

A study of patients with acute dysentery revealed unexpected findings in the small intestine. From a clinical viewpoint, one might expect, with the frequent bowel movements in dysentery, that transit time or motility in the small intestine would be

unusually rapid and therefore the barium meal would rush through the small and large bowel to be evacuated in a very short period of time. One might also expect to find the tone of the intestine increased. A tendency to hypertonicity was observed. The motility in the majority of the instances was definitely delayed almost to the point of actual stasis despite the presence of frequent stools during the period of examination. It was interesting to observe that the barium column moved normally through the jejunum but then puddled in the pelvic loops of ileum. In view of this delay in distal progression of the meal, one might expect to find a definitely hypotonic or "lazy" bowel but, as compared with a group of normals, the ileal loops appeared shortened and essentially normal in caliber. The explanation for the delayed motility is lacking.

FRANZ J. LUST

METABOLISM AND NUTRITION

YOUNG, N. F., ABELS, J. C., AND HOMBURGER, F. Studies on carbohydrate metabolism in patients with gastric cancer. Defective hepatic glycogenesis; effects of adreno-cortical extract. *J. Clin. Invest.*, 27: 760 (Nov.) 1948.

Of the several metabolic dysfunctions known to be present in patients with gastric cancer, that pertaining to carbohydrate foods was studied here. It was found that glucose, administered by stomach tube to patients with gastric cancer, is not transformed into hepatic glycogen, and that this defective glycogenesis can be corrected by the administration of adrenal cortical extract. This disturbance of carbohydrate metabolism differs from that found in adrenalectomized animals. Insulin has no effect on the disturbed glycogen metabolism from administered dextrose. The abnormality is independent of the existence of tumor metastases in the liver or elsewhere and there is no relationship between the size of the tumor mass and the severity of the disturbance. The prompt amelioration of this defect, by the simultaneous preoperative administration of glucose and adrenal cortical extract, would seem to indicate the use of these measures to prepare patients for major

abdominal operations, especially for surgery in gastric cancer.

SAM OVERSTREET

SCHLOSS, E. M. Physicochemical changes in intestinal obstruction. *Med. Clinics N. Am.*, 1717 (Nov.) 1948.

The basic conditions accounting for the physicochemical changes in intestinal obstruction are explained, and treatment is suggested. Distension proximal to the site of obstruction, and loss of electrolytes are the operating factors. Distension stimulates glandular secretion, thus precluding the interchange of fluids and electrolytes, in addition to causing emesis. Gastric, duodenal, pancreatic, or hepatic secretion may be lost, depending on the level of obstruction. Relief of distension is frequently accomplished by intubation, which in turn leads to loss of fluid and electrolytes. Pyloric obstruction results in dechlorination and dehydration. The chain of events leading to dehydration begins with loss of chlorides, stimulating compensatory rise in carbon dioxide and bicarbonate. Further increase of carbon dioxide and bicarbonate leads to alkalosis, bringing the compensatory kidney mechanism of sodium excretion into play. Thus, fixed base is lost, which cannot be compensated. Loss of electrolytes results in dehydration and reduction of blood plasma volume. Reduced filtration pressure of the kidneys accounts for impaired function and increase of blood nonprotein nitrogen. Administration of saline solution will correct alkalosis. Sometimes, however, the chlorides are unable to displace enough bicarbonate, and intravenous administration of ammonium chloride is indicated. Should the loss of pancreatic and intestinal secretions exceed the loss of gastric juice, acidosis may develop; resulting dehydration is corrected by administration of saline solution. Ketosis, the result of starvation, may be associated with alkalosis as well as with acidosis, and requires administration of glucose.

L. T. ROSENTHAL

SELLERS, E. A. Dietary factors and hepatic injury. *Can. Med. Assoc. J.*, 59: 403 (Nov.) 1948.

Cirrhosis can be produced consistently by prolonged feeding of diets low in choline

and its precursors. The author believes there is acceptable evidence for regarding dietary cirrhosis as a choline-deficiency disease. Massive lobar necrosis has been produced by feeding, to rats, diets low in the sulphur-containing amino acids. This is not a consistent finding, and the relationship of methionine and cystine to the disease is not clear. At present their lack must be regarded as a contributory rather than a causal factor. A remarkable degree of repair may take place in experimental cirrhosis produced by carbon tetrachloride. Choline or its precursors are considered necessary in the repair process. There is no evidence that combinations of the lipotropic factors, or increased total intake of these substances, cause a greater degree of recovery than the presence of an adequate amount of a single lipotropic factor in an otherwise adequate diet.

JOSEPH B. KIRSNER.

PHARMACOLOGY

LOEWE, S. Studies on the laxative activity of triphenylmethane derivatives. *J. Pharmacol. Exp. Therap.*, 94: 288 (Nov.) 1948.

From a study of the laxative action of 46 isomers and homologs of phenolphthalein in monkeys, it was shown that the laxative action is not caused by irritation by a phenolic group. The variations in activity with various substitutions in the benzene nuclei and blocking of hydroxyl groups, led to some tentative rules which are based on spatial arrangement and intramolecular kinetics. The maximal potency, 1.63 times of phenolphthalein, was found in the racemic trihydric pyrogallolbenzenephthalein, which suggests a still higher potency in an optical isomer. Enlargement of the benzene part of the skeleton by substitution decreased the potency. A decrease was observed generally by replacement of the phthalide by phthalimide, N-methylphthalimide or anthrone, an increase by replacement with isatin, N-acetylisatin or naphthalide. Phenolnaphthalein had 5 and the isatins 17 times the potency of phenolphthalein.

ARTHUR E. MEYER.

MISCELLANEOUS

HERFORD, R. A. AND STANDARD, S. Oral streptomycin in surgery of the large bowel.

The production of secondary hypoprothrombinemia. *Ann. Surg.*, 128: 987 (Nov.) 1948.

The influence of streptomycin, given orally, on stool bacterial counts and on blood prothrombin time was tested on 4 normal subjects. Each subject received 1 gm. of streptomycin in a glass of water 3 times daily for 14 days. There was no modification made in the diet. The prothrombin time and stool bacterial count were determined 24 hours after beginning the streptomycin by mouth and at 48- to 72-hour intervals thereafter for 14 days. In all subjects the maxi-

mum reduction in stool bacterial count was achieved within 48 hours of the institution of the antibiotic drug. The whole plasma prothrombin time was increased an average of but 4 seconds (e.g., 17 seconds to 21 seconds). The 12.5 per cent diluted plasma prothrombin time was increased an average of 19 seconds. It is recommended that synthetic Vitamin K be given surgical patients receiving oral streptomycin before and after operation to prevent the appearance of hypoprothrombinemia.

LEMUEL C. MCGEE.

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ELECTROPHORETIC STUDIES OF THE SERUM PROTEINS IN PORTAL CIRRHOSIS*

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The electrophoretic patterns of the serum proteins in portal cirrhosis and other hepatic diseases have been described by numerous authors¹⁻¹⁰. The present study of 14 proven cases of portal cirrhosis was undertaken to investigate the relationship between the electrophoretic pattern and the clinical findings. A subsequent report will consider the alterations of the electrophoretic pattern during the course of medical management of portal cirrhosis¹¹.

METHODS

Electrophoretic runs were performed with the standard apparatus and technique described by Longsworth¹². Sodium diethylbarbiturate (veronal) buffer of pH 8.6 and ionic strength 0.1 was used. After dialysis against the buffer, the serum was diluted with buffer solution to four times its original volume prior to dialysis. Electrophoresis was carried out at approximately 1.5° C. for 120 minutes at a potential gradient of 7.7 volts per centimeter.

All photographs were taken by the schlieren scanning method. In the estimation of the fractions as per cent of the serum proteins both ascending and descending patterns were used, the areas being divided by ordinates from the nadirs between peaks to the base lines. The quantities of the fractions in grams per cent represent the products¹³ of the percentages and the total proteins from the conventional Kjeldahl method, neglecting recent theoretically valid refinements¹⁴⁻¹⁶.

Serum bilirubin¹⁷, total proteins by the Kjeldahl method, albumin and globulin by a modification of the Howe method, alkaline phosphatase in Bodansky units¹⁸, bromsulfalein retention¹⁹, thymol turbidity (buffer pH 7.55), and cephalin-cholesterol flocculation²⁰ tests were done simultaneously with electrophoretic analyses.

CASE MATERIAL

The fasting sera of ten volunteer medical students and physicians were studied as normal controls. All control subjects had findings within the normal

* This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, of the American Medical Association.

range in the hepatic function tests listed above, and in addition normal prothrombin time, cholesterol and esters, hippuric acid excretion and 24-hour urinary and fecal urobilinogen.

The 14 patients with portal cirrhosis were selected from larger clinical material, the series being limited to proven cases. Histologic confirmation of the diagnosis was obtained by laparotomy biopsy or needle (Vim-Silverman) biopsy in 12 of the 14 patients. In one clinically typical case (P. F.) the cirrhotic liver was visualized by periotoneoscopy and subsequently during an umbilical heriorrhaphy, but tissue for biopsy was not obtained. In one case (A. S.) the diagnosis was based upon the clinical features of jaundice, hepato- and spenomegaly, spider angiomata, edema and ascites.

TABLE I
Normal sera

	ELECTROPHORETIC DATA											HOWE SODIUM SULFATE				
	Per cent					Grams per cent					A/G	A/G	Grams per cent			
	Al	α_1	α_2	β	γ	Alb	α_1	α_2	β	γ			Alb	Glob	Tot	
1	63.3	2.5	8.8	12.0	13.5	4.52	0.18	0.63	0.86	0.96	1.73	2.43	5.06	2.08	7.14	
2	61.1	3.3	9.1	12.7	13.9	4.70	0.25	0.71	0.98	1.07	1.57	2.38	5.43	2.28	7.71	
3	60.0	4.7	10.6	14.3	10.4	3.93	0.31	0.70	0.94	0.68	1.50	2.32	4.58	1.98	6.56	
4	60.6	3.6	8.5	13.2	14.1	4.07	0.24	0.57	0.89	0.95	1.54	2.95	5.02	1.70	6.72	
5	61.3	4.6	9.5	13.4	11.2	4.18	0.31	0.65	0.91	0.77	1.58	2.67	4.96	1.86	6.82	
6	55.0	4.6	12.9	13.2	14.3	3.80	0.32	0.89	0.91	0.99	1.22	1.93	4.55	2.36	6.91	
7	56.8	5.3	11.3	13.7	12.9	4.02	0.38	0.80	0.97	0.91	1.32	1.77	4.52	2.56	7.08	
8	64.8	4.5	9.2	9.9	11.6	4.53	0.32	0.64	0.69	0.81	1.84	2.41	4.94	2.05	6.99	
9	58.6	3.6	9.6	12.1	16.1	4.06	0.25	0.66	0.84	1.11	1.42	1.97	4.59	2.33	6.92	
10	61.9	3.0	7.3	13.2	14.6	4.48	0.22	0.53	0.95	1.06	1.63	2.55	5.20	2.04	7.24	
Average.....	60.3	4.0	9.7	12.8	13.2	4.23	0.28	0.68	0.89	0.93	1.52	2.31	4.89	2.12	7.01	
Standard Deviation..	2.8	0.8	1.5	1.2	1.7	0.29	0.06	0.10	0.08	0.13	0.18	0.34	0.30	0.24	0.30	

Ten of the 14 cases were chronic alcoholics; in four (R. D., A. S., I. B., and M. D.), no history of alcoholism could be elicited.

The electrophoretic analyses and liver function tests were performed before or very early in the course of medical management. Although a few patients had received some form of therapy elsewhere prior to study, none had systematically followed an adequate dietary regime for any appreciable period. Consequently, the data are regarded as representing the findings in untreated portal cirrhosis.

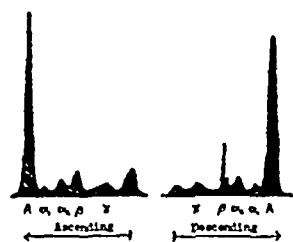
The cases were divided into two groups: seven with ascites and seven without clinical evidence of ascites. In the latter group three patients manifested no clinical symptoms of hepatic disease and the diagnosis was made by chance;

* Starred values not simultaneous with other data.

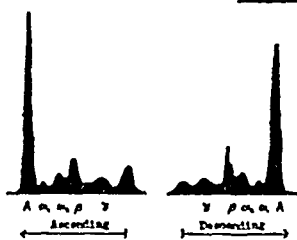
• Starred values not simultaneous with

in one instance (M. M.) hepatic cirrhosis was an incidental laparotomy finding, and in the other two (J. C. and D. B) it was established by needle biopsy of the liver done because of the finding of an enlarged liver on physical examination. These three patients were regarded as having "latent" portal cirrhosis, histologically verified.

PORTAL CIRRHOSIS WITHOUT ASCITES



NORMAL SERUM

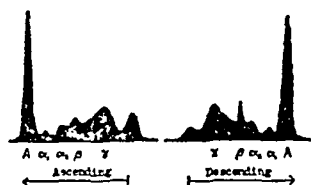


D.B. - Nearly normal pattern. Normal serum bilirubin. No clinical symptoms. Marked fibrosis and fatty infiltration histologically.

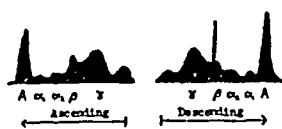


I.B. - Markedly abnormal pattern. Elevated serum bilirubin.

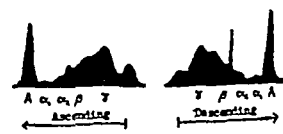
PORTAL CIRRHOSIS WITH ASCITES



A.S. - Markedly abnormal pattern. Elevated serum bilirubin.



M.S. - Extremely abnormal pattern. Gamma-globulin exceeds albumin. Elevated serum bilirubin.



J.B. - Extremely abnormal pattern. Unusual beta-globulin peaks. Gamma-globulin exceeds albumin. Elevated serum bilirubin.

FIGURE 1. The albumin peaks are indicated by "A", and the globulins by their respective Greek letter prefixes. The unlabelled peaks are the stationary anomalous boundaries due to gradients of buffer salt.

RESULTS

The electrophoretic and chemical data on the serum proteins of the ten normal volunteers are listed in Table I. The findings are comparable with those of other workers^{10, 13, 15}.

As shown in Table II, all cases of portal cirrhosis with ascites presented markedly abnormal electrophoretic patterns. In both per cent compositions and absolute amounts there were striking diminutions of the albumin fractions and elevations of the gamma-globulin fractions to double or even triple the normal values, so that in four of the seven cases with ascites the gamma-globulin actually exceeded the albumin. A less frequent abnormal finding was elevation of the beta-globulin; in J. K. and J. B. the beta-globulin was

TABLE III
Portal cirrhosis without ascites

		ELECTROPHORETIC DATA												HOWE SODIUM SULFATE				BILIRUB		CEPH	THYM	ALK PHOS	BSP %
		Per cent						Grams per cent						A/G	Grams per cent		Dir	Tot					
		Alb	α ₁	α ₂	β	γ	Alb	α ₁	α ₂	β	γ	Alb	Glob		Tot								
I. B.	36.9	8.0	9.1	16.9	29.1	2.70	0.58	0.67	1.24	2.13	0.58	0.79	3.23	4.09	7.32	0.9	1.5	4+	17.6	4.4	48		
G.K.	37.7	6.0	10.4	23.7	22.2	2.89	0.46	0.80	1.82	1.71	0.60	0.84	3.50	4.18	7.68	1.7	3.5	1+	8.0	4.0	—		
B.K.	48.1	3.8	15.5	8.3	24.3	3.58	0.28	1.15	0.62	1.81	0.93	1.46	4.42	3.02	7.44	1.0	2.0	4+	14.1	10.0	14		
M.D.	50.0	5.2	6.6	15.9	22.3	3.15	0.33	0.42	1.00	1.40	1.00	1.74	4.00	2.30	6.30	0.8	1.8	3+	9.0	7.3	—		
J. C.	55.1	5.9	14.3	13.7	11.0	3.61	0.39	0.94	0.90	0.72	1.23	1.07	3.41	3.15	6.56	—	—	1+	5.3	—	6		
M.M.	52.2	4.0	10.4	18.6	14.8	4.14	0.32	0.83	1.47	1.17	1.09	1.61	4.89	3.04	7.93	0.2	0.6	neg.	11.7	3.0*	33		
D. B.	55.2	4.5	10.3	17.8	12.2	3.99	0.33	0.74	1.29	0.88	1.23	1.91	4.75	2.48	7.23	0.2	0.7	neg.	4.5	5.7	38		
Average.....	47.9	5.4	10.9	16.4	19.4	3.44	0.39	0.79	1.19	1.40	0.95	1.35	4.03	3.18	7.21								
Standard Deviation.....	7.0	1.3	0.9	4.2	6.4	0.56	0.10	0.21	0.37	0.48	0.25	0.40	0.62	0.67	0.52								

* Starred values not simultaneous with other data.

almost as high as the gamma-globulin, in the latter case exhibiting bizarre double peaks (see Figure 1).

The three patients without clinical symptoms of liver disease ("latent" cirrhosis), J. C., M. M., and D. B., had serum protein compositions quite close to the normal range (Table III).

The other four patients without ascites but with clinically evident portal cirrhosis manifested alterations of the serum protein composition similar in character to those in the group with ascites, but varying from moderately abnormal in M. D. to markedly abnormal in I. B. The patients without clinical evidence of ascites tended to have considerably higher albumin values than the group with ascites.

DISCUSSION

In agreement with the findings of previous authors¹⁻¹⁰, the present study demonstrates characteristic alterations in the serum proteins in untreated portal cirrhosis: diminution of the albumin fraction and elevation of the gamma-globulin fraction, and, somewhat less frequently, elevation of the beta-globulin fraction.

That a relation exists between the degree of abnormality of the serum proteins and the clinical evidence of hepatic insufficiency cannot be more than suggested by the present findings. The problem will be considered more fully in a separate report on the alterations of the electrophoretic pattern during the course of medical management¹¹. It may be noted, however, that the only nearly normal electrophoretic patterns occurred in patients without clinical symptoms of hepatic disease, i. e. "latent" cirrhosis.

As expected, the cases with ascites showed lower albumin values than those without clinical evidence of ascites.

Comparison of the alterations of the serum proteins with the various tests of hepatic function performed simultaneously fails to reveal any clearly evident direct correlation.

SUMMARY

1. Electrophoretic analyses of the serum proteins of 14 proven cases of portal cirrhosis revealed pronounced deviations from the normal composition.

2. The principal abnormalities consisted of diminutions of the albumin fractions and elevations of the gamma-globulin fractions. Less frequently observed were elevations of the beta-globulin fractions.

3. The patients with ascites tended to have considerably lower albumin values than patients without ascites.

4. Three cases without symptoms of hepatic disease ("latent" portal cirrhosis) had serum protein compositions quite close to the normal range.

The authors wish to express their gratitude to Doctor E. S. Guzman Barron for making available the electrophoretic apparatus used in this study.

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THE DUMPING SYNDROME: WHAT MAKES IT AND HOW TO AVOID IT

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Of late some men have claimed that the dumping syndrome is due to a depression of the titer of sugar in the blood. Others have been unable to confirm this. Even if they had, it would have been very difficult for me to believe that a lowered blood sugar content could have anything to do with the dumping syndrome. The symptoms appear too soon after the food enters the jejunum.

First, it should be noted that the syndrome is not dependent on the presence of a gastro-enteric anastomosis or a gastric resection. This fact immediately invalidates a lot of the theorizing that has been done. In 1914 I saw a frail, overly sensitive, migrainous girl. She appeared to have inherited from psychotic relatives a hair-trigger sort of autonomic nervous system which often played tricks with her heart, her blood vessels, her stomach, her kidneys or her skin. She got the dumping syndrome whenever she drank quickly a glass of ice water or cold milk. When I gave her a large glass of cold milk containing a little barium I could see with the roentgenoscope that the fluid ran right out through an open pylorus and down into the jejunum. As soon as it reached the bowel, and long before any change could take place in her blood, she went into a state of mild shock. This, evidently, was due to the physical stimulus of the cold fluid on the inner surface of the bowel. When I gave her water or milk slowly, and especially after a piece of buttered toast, which had somewhat closed the pylorus, she had no trouble.

In the thirty-five years since then, I have seen many other hypersensitive and overly reactive persons with tremendously exaggerated knee jerks, who got a distressing dumping syndrome after a meal—apparently because their reflexes were so exaggerated. Again, this syndrome came so soon after eating that the impression was that the nerves must have been stimulated mechanically.

Then I found some persons who got a dumping syndrome right after taking some fluid to which they were allergically sensitive. I, for instance, can get the typical syndrome with nausea and sweating, feelings of great warmth, and epigastric all-goneness a few minutes after drinking a cup of chocolate to which I happen to be allergically sensitive.

In 1914 I learned much about the dumping syndrome while working with 2 persons who had a feeding jejunal stoma. Again, my strong impression was that the symptoms were reflex and due to mechanical, physical or chemical stimulation of the jejunal mucosa. If I fed the patient slowly by the drip

method, with food at body temperature and fairly isotonic, he had no distress, but if I ran in ice water to get a thermal stimulus, or if I ran in an isotonic solution of sodium chloride rapidly, to produce a mechanical stimulus, or if I ran in a hypertonic solution of glucose to get a physicochemical stimulus, the patient was distressed and broke into a sweat.

Later I studied the important factor of individual hypersensitiveness which was well illustrated by 2 almost psychopathically hypersensitive women, mother and daughter. Each had been unfortunate enough to undergo subtotal resection for what appeared from the story to have been a functional type of abdominal distress. Each of them suffered for the next ten years or so with a severe dumping syndrome. I think it more than a coincidence that the 2 women with the worst and the most prolonged suffering from the dumping syndrome that I ever saw were mother and daughter. In both of these women the distress eventually quieted down, probably because the jejunal mucosa became toughened and less sensitive.

One of the best bits of evidence to show that the dumping syndrome can be produced purely through exaggerated reflexes is the fact that I have seen it in a number of nervous and psychopathic persons who got it when their bowels moved. Some of them went all to pieces nervously after a bowel movement which apparently sent a storm through the same nerves which cause the type of dumping distress that originates in the jejunum.

WHAT TO DO?

Obviously, the logical treatment for the dumping syndrome after an operation is to try to get the person into a less irritable state. Then it helps if the person will eat while resting and reclining. It helps greatly to give first some dry toast "to plug the hole"; it helps to eat slowly; to avoid liquids at mealtime, to keep the food at body temperature, and to keep it fairly isotonic. As one would expect, many patients say that the addition of much sugar causes distress. Water at body temperature can be drunk slowly between meals.

SUMMARY

The dumping syndrome can be seen in hypersensitive, overly reactive or psychoneurotic persons who have not had any operation on the stomach. In them, it appears to be due to the rapid outpouring of food through a patulous pylorus.

Quite a few hypersensitive persons with exaggerated reflexes get a dumping syndrome right after eating. Some persons get it if they drink some fluid like chocolate to which they are allergically sensitive.

One can easily produce the dumping syndrome in a minute by running food into a jejunal fistula, too fast, too cold, or too full of sugar.

The worst 2 instances of the dumping syndrome observed by the writer were met with in a mother and daughter, both hypersensitive and neurotic. The dumping syndrome is produced in some overly sensitive persons by a bowel movement. This shows that it is due to a storm in autonomic nerves.

The logical treatment for the dumping syndrome is, then, (1) to quiet nerves by rest, (2) to give food while the person is reclining quietly, (3) to avoid fluids at mealtime, (4) to give first a piece of dry toast "to plug the hole," (5) to eat slowly, (6) to take the food at body temperature, and (7) to keep it fairly isotonic by avoiding much sugar.

SEX AS A CONSTITUTIONAL FACTOR FOR SUSCEPTIBILITY TO PEPTIC ULCER

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INTRODUCTION

Prior to 1905 many reports of mortality and clinical statistics showed that peptic ulcer usually occurred most frequently in the stomachs of women under thirty years of age¹. Since 1905 similar statistical reports have shown that peptic ulcer occurs more frequently in men than in women regardless of whether the ulcer is located in the stomach or duodenum. Tight lacing was discontinued between 1900 and 1905, and hence may have been the cause of the high incidence of gastric ulcer in the young women. Regardless of the once high incidence of gastric ulcer in young women, it is certain that today more men than women have peptic ulcer.

It is obviously significant to know why men have the disease more frequently than women. When one considers this problem numerous questions arise. The major questions are:

I. Do men more frequently contract the disease (a) because they are constitutionally more susceptible, or (b) because they are exposed more frequently to environmental conditions which excite the disease?

II. If men are constitutionally more susceptible does the susceptibility appear (a) before or (b) after puberty, that is before or after the production of a relatively large amount of sex hormones.

Since there is no evidence pertaining to a sex difference in the incidence of peptic ulcer in animals, this phase of the problem must for the present be confined to an accumulation of evidence in man. So, the present study was undertaken to ascertain whether mortality statistics may contribute to the answer of the above questions.

PRESENTATION OF DATA

The available mortality statistics of the United States², Great Britain³, Sweden⁴, and Switzerland⁵ were consulted.

The sex ratios of deaths from peptic ulcer and from all causes according to age groups are shown in Table 1. The data for the four countries are combined for certain age groups in Table 2. The data are combined chiefly to increase the number of deaths from peptic ulcer in the age groups below 20 years of age. These data illustrate several significant points.

First, the ratio of male to female deaths from peptic ulcer from birth to 14 years of age is approximately 1.3, and from 15 to 19 years is 2.84. That is, a

TABLE 1
Ratio of Male to Female Deaths for Various Age Groups

SOURCE	DEATHS	AGE GROUPS																				
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99	100+
U. S. 1934-44	A	1.46	2.2	0.87	2.88	4.70	4.83	5.5	6.95	7.15	6.24	6.2	6.75	6.55	3.9	3.16	2.4	2.5	1.47	1.14	1.05	0.33
	B	1.39	1.34	1.51	1.48	1.37	1.20	1.23	1.32	1.44	1.52	1.61	1.60	1.47	1.38	1.21	1.10	0.99	0.86	0.72	0.59	0.49
G. B. 1927-37	A	0.91	2.2	1.89	2.48	4.15	5.53	5.65	4.6	3.83	3.93	3.67	3.56	2.75	2.29	2.0	1.62	1.09				
	B	1.29	1.15	1.07	0.98	1.10	1.01	0.99	1.05	1.13	1.21	1.23	1.27	1.23	1.14	1.0	0.87	0.24				
Sweden 1923-44	A	2.0	0.14	0.66	3.0	3.23	3.8	2.98	3.9	3.75	5.0	5.7	7.15	6.95	7.6							
	B	1.33	1.2	1.05	1.08	1.19	1.07	1.07	1.02	1.02	1.05	0.47	1.11	1.09	0.79							
Swiss 1927-30	A	0.0±	1.5	3.5	3.68													80+				
	B	1.32	1.13	0.99	1.0																	

(A) Male: Female Ratio for Deaths Due to Peptic Ulcer.

(B) Male: Female Ratio for Deaths Due to All Causes

± Infinity, as four female deaths occurred, with no male deaths in this group.

TABLE 2
Data for U. S. A.; Great Britain, Sweden and Switzerland Combined

DEATHS		AGE GROUPS											
		0-4		5-14		15-19		20-29		60-69		70+	
		No.	Ratio	No.	Ratio	No.	Ratio	No.	Ratio	No.	Ratio	No.	Ratio
Peptic Ulcer	Male	159		120		482		3620		17238		16335	
	Female	125	1.26	93	1.29	173	2.84	859	4.22	6924	2.44	7845	2.09
All Causes	Male	1,168,278		231,110		168,865		435,756		2,252,290		3,699,029	
	Female	862,674	1.35	180,737	1.28	132,437	1.26	362,526	1.20	1,705,071	1.32	3,840,464	0.97

two fold, statistically significant ($\chi^2 = 7.7$), increase in the ratio occurs during the first five years after puberty. The ratio further increases so that between 30 and 60 years of age approximately 6 males die of peptic ulcer to 1 female.

So these data show that shortly after the onset of puberty some factor begins to operate to cause the mortality from peptic ulcer to increase to a greater extent in man than in woman.

Second, more males than females die from peptic ulcer at all ages. This holds also for the first two weeks after birth.

This general observation has no etiological significance because more males than females die from all causes at all ages up to 60 or 70 years of age. (It is generally true biologically that more males than females are born and the male is more susceptible to disease than the female⁵.) A glance at Tables 1 and 2 will show that the sex ratio for deaths from peptic ulcer under the age of 15 years is approximately the same as that for all causes. Thus, the greater number of male deaths from peptic ulcer under 15 years of age is very probably only a reflection of the greater general susceptibility of the male to death from all

TABLE 3

Comparison of Deaths from Peptic Ulcer, Appendicitis, and All Causes in the U.S. from 1934 to 1944 presented According to the Sex Ratio

CAUSES	AGE GROUPS			
	0-4	5-14	15-19	20-24
Appendicitis.....	1.35	1.28	1.65	1.63
Peptic Ulcer.....	1.46	1.27	2.84	4.70
All causes.....	1.39	1.41	1.48	1.37

diseases, and it is not due to an inherently greater susceptibility of the male infant to peptic ulcer.

To examine this deduction the sex ratio of deaths from appendicitis was determined and the results are presented in Table 3. It will be noted that during the first four years of life more males than females die from appendicitis, and that the number of males who die in excess of females is approximately the same for peptic ulcer, appendicitis and all causes. The same is true for deaths from enteritis and all diseases of the alimentary tract, though for lack of space the data will not be presented. Though the deaths of males from appendicitis increase after puberty slightly more than those of females, the increase of male deaths from peptic ulcer is strikingly greater by contrast.

DISCUSSION

Clinical data on the incidence of peptic ulcer in infants and children have been reported; but in view of the reason for or method of collection of the

cases their reliability for the purpose of this study is more open to question than mortality statistics. For example, Bird, Lemper and Meyer⁷ who were primarily interested in the results of surgery, collected 243 cases of peptic ulcer in children under 15 years of age. Of these, 126 were males and 80 females, but in 37 the sex was not mentioned. Saltzstein, Farbman and Sandweiss⁸ collected 105 cases from the literature between the ages of 1 and 12, the ulcer being proven by X-ray, operation or autopsy. There were 57 males and 48 females, or a M:F ratio of approximately 1.2:1. They excluded ulcers under one year of age because Kennedy; believed ulcers under 1 year of age were different in type from those occurring later. However, the U. S. Mortality data² show that the M:F ratio of 0 to 1 year is 1.46:1 and from 0 to 4 years is also 1.46:1.

The greater susceptibility of the male infant and child to peptic ulcer is best explained by assuming that it is due to an inherent constitutional difference which renders males more susceptible to most diseases. At puberty, however, something occurs which causes the male to die of peptic ulcer many times more frequently than the female.

It is reasonable to suppose that this difference is due to the action of the sex hormones. However, it has not been clearly ascertained what effect the male (testosterone) and female (estrone) hormones have on gastric secretion and motility in the human. It is known that from approximately 15 to 60 years of age a man on the average secretes more acid in response to a test meal than a woman¹⁰. Whether this is due to sex hormones, to the social factor which imposes more responsibilities on the male or to some other factor is uncertain.

Pregnancy usually causes a remission in peptic ulcer, and antuitrin-S obtained from human pregnancy urine has a prophylactic effect against Mann-Williamson postoperative jejunal ulcers in the dog¹¹. It could reasonably be assumed therefore that pregnancy contributes to the cause of the smaller number of deaths from peptic ulcer in women. But it has not been demonstrated that the urine extract from pregnant women is distinctly more effective than the urine extract from non-pregnant women. Urine extracts from women (pregnant and non-pregnant) are distinctly superior to those from men.

Such an assumption, however, is not permitted by the data in Table 4 showing mortality statistics from peptic ulcer in England¹². In England the death certificate carries the social or income class of the deceased. Referring to Table 4, it will be noted that the death rate from peptic ulcer in male and female in the laboring class, or Class 5, who suffer principally from gastric ulcer¹² is approximately the same; but, in Class 1, or the high income group where duodenal ulcer predominates, the death rate from peptic ulcer is much higher in the male. Furthermore, far more women in the laboring class die of peptic ulcer than in the high income group (12). And, there are, moreover, more

pregnancies in the women in the laboring class, as is well known¹³. This would suggest that when the strains of living are approximately the same in the two sexes the incidence of deaths from peptic ulcer is also approximately the same.

Since the male is inherently or biologically more susceptible to peptic ulcer, as well as most diseases of the alimentary tract²⁻¹⁴, it is reasonable to assume that the alimentary tract of the male is more susceptible to the strains or tensions of living. We interpret the evidence presented as indicating that more men than women die of peptic ulcer because the human male is constitutionally more susceptible to most diseases of the alimentary tract and because he is more frequently exposed to the strains and tension which excite peptic ulcer.

TABLE 4
*Mortality from Peptic Ulcer in Relation to Social Class**
All Classes = 100 at ages 35-65 (1930-32)

CLASS	CLASSES DESCRIBED	MARRIED WOMEN	ALL MEN	SINGLE WOMEN
1	Professional and Nobility	53	72	80
2	Managers	98	87	
3	Skilled	99	101	
4	Semi-skilled	99	102	123†
5	Unskilled	118	118	

* Ref. 12

† Seventy-four per cent of all unmarried women were in Class 3 and most were under 35 years, demonstrating the effects of increased strain of living in women.

SUMMARY

The mortality statistics of the United States, Britain, Sweden and Switzerland were reviewed to determine if any difference in the sex incidence of peptic ulcer occurred. No statistically significant difference was found before fourteen years of age between the sexes. After this age the difference became marked. The significance of these findings, and their relation to sex hormones and environmental stresses is discussed. It is concluded from these statistics that a constitutional factor is involved in the greater incidence of peptic ulcer in the male, which is evident prior to but is emphasized after the age of puberty.

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STUDIES WITH BROMSULFALEIN

II. FACTORS ALTERING ITS DISAPPEARANCE FROM THE BLOOD AFTER A SINGLE INTRAVENOUS INJECTION

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The disappearance of Bromsulfalein (BSP) from the blood after single intravenous injections was discussed in a previous paper¹. Further studies on the mechanisms responsible for removal of the dye have been carried out in normal and hospitalized subjects given single injections of BSP before, simultaneously, and after various procedures designed to alter the rate at which the dye disappears from the blood. Since repeated tests under controlled conditions were necessary, the number of subjects studied in each group has not been large, and statistical evaluation of the data has not been carried out.

METHODS

Studies of Bromsulfalein disappearance were carried out with the aid of techniques previously described¹. In a number of tests hepatic venous samples, obtained by the method of hepatic vein catheterization², were obtained simultaneously with peripheral venous samples. In comparing the concentrations of BSP in peripheral with hepatic venous blood, the following abbreviations have been used:

1. P = Concentration of BSP in mgms. per 100 ml. peripheral venous plasma.

2. H = Concentration of BSP in mgms. per 100 ml. hepatic venous plasma.

3. P - H = amount of BSP in mgms. extracted from each 100 ml. plasma as it passes through the liver.

4. $\frac{P - H}{P}$ = Extraction ratio, the ratio between the amount of BSP extracted by the liver from each 100 ml. of plasma and the concentration of BSP in peripheral venous blood.

5. EHBF = estimated hepatic blood flow (ml./min.)

6. PDR = percentage disappearance rate for BSP (based upon the change of BSP concentration in peripheral venous blood unless otherwise indicated).

7. "Saturation" = A progressive decrease in PDR, evidenced graphically by curvilinearity (i.e. a flattening out) of the slope representing PDR.

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RESULTS

Repeated tests. Table I indicates that repeated BSP tests under comparable conditions yield reproducible results. One normal subject was tested 5 times

TABLE I
Normal subjects

SUBJECT	FIRST TEST PDR	SECOND TEST WITHIN 5 DAYS	SUBJECT	FIRST TEST PDR	SECOND TEST WITHIN 5 DAYS
J. L.	16.75	16.5	S. K.	13.6	13.6
R. C.	11.8	12.4	A. C.	15.5	16.0
R. S.	12.5	13.3	F. I.	14.1	14.0
P. L.	11.5	10.5	A. M.	12.7	12.6

Cirrhotic subjects

SUBJECT	FIRST TEST PDR	3 MONTHS LATER PDR	6 MONTHS LATER PDR	18 MONTHS LATER PDR
L. F.	4.5	4.4	4.2	4.5
E. B.	4.9	5.0	5.0	
L. B.	3.0		3.7	
F. C.	2.0		2.2	

Reproducibility of BSP tests. Tests were performed with subjects sitting or lying quietly; only a few were fasting. The cirrhotic subjects had chronic, relatively stationary liver disease without clinical icterus but with evident portal hypertension.

TABLE II

SUBJECT	PDR CONTROL	PDR DURING EXERCISE
E. B.	16.8	16.6
D. F.	16.5	13.4
J. L.	16.5	12.4
P. A.	15.3	9.1
I. R.	13.35	13.1
R. S.	13.3	12.1
R. C.	12.4	12.6
D. R.	10.8	7.3

Effect of exercise. Control tests were carried out in normal fasting subjects who were resting (either seated or supine) during and for 15 minutes preceding the test. For the exercise test (carried out at least 2 days later), the subject first hopped for 2 minutes on one leg, then was given the dye, and, for the next 30 minutes, walked up and down 4 flights of stairs at a rate sufficient to produce tachycardia, sweating, and mild dyspnea.

within 12 months; the following PDRs were obtained: 14.0, 14.1, 13.45, 13.2, 14.0.

Effect of exercise and eating. The results reported in Table II indicate that PDR is variably reduced by strenuous exercise (moderately rapid stair climbing

during the 30 minutes required by the test). This reduction appears most noticeable in those with a rapid PDR during the control period. Table III suggests that eating either normal or high caloric meals does not change PDR significantly.

Comment. According to Bradley³, exercise decreases hepatic blood flow in man, but Herrick et al⁴ found that in animals exercise either does not change or increases blood flow in the superior mesenteric artery, splenic artery, and splenic vein. The effects of digestion on hepatic blood flow also require further study. Herrick et al⁵ observed that venous outflow from the canine liver increased after a meal, and liver lymph flow has been shown to be greatly increased following digestion⁶. Studies carried out in man with the BSP method have not shown any significant change in blood flow following intravenous administration of glucose⁷.

On the reasonable assumption that both exercise and eating may affect hepatic blood flow, why does PDR frequently remain unchanged in spite of

TABLE III

SUBJECT	PDR FASTING	PDR p.c.	TYPE OF MEAL	TIME INTERVAL p.c.
				hours
A. R.	10.3	10.8	Normal breakfast	2
M. B.	10.2	10.2	Normal breakfast	2
G. B.	12.6	11.7	Normal breakfast	1
F. I.	14.1	14.0	150 gms. butter	4
D. B.	10.7	10.7	150 gms. butter	4
F. H.	14.9	14.1	150 gms. butter	4

Effect of eating. Normal, resting subjects were used.

these activities? Presumably, an inverse relationship obtains between the liver's blood flow and the extraction ratio; i.e., as hepatic blood flow increases, the proportion of dye extracted by the liver decreases, thereby maintaining a constant PDR in the face of circulatory changes. The validity of such an inverse relationship is assumed in the BSP method of estimating hepatic blood flow², for, given a constant removal rate, EHBF is inversely proportional to the amount of BSP removed from each 100 ml. of plasma.

If an inverse relationship exists, it presumably holds only within certain limits and does not apply to gross circulatory changes. A very slow blood flow, for example, would not insure 100% extraction of the dye; and, as shown in Table II, the circulatory adjustments that attend moderately strenuous exercise may be sufficient to reduce PDR, particularly in those subjects who, while resting, have an unusually rapid removal of the dye. Within such ranges of hepatic blood flow as may be induced by eating or moderate exercise, however, an inverse relationship apparently may obtain.

In tests utilizing a constant infusion of BSP, the removal rate, the extraction ratio, and EHBF decrease when the subject is tilted from the supine to the upright position⁸. These results have been construed to mean that routine BSP tests should be carried out only in supine patients. The changes in blood flow induced by tilting a passive subject are often of such magnitude, however, that they easily may exceed the range over which the inverse relationship holds.* The circulatory changes that attend strenuous exercise appear likewise sufficient to change the results of BSP tests. Minimal activity, on the other hand, appears less likely to alter PDR significantly. It is suggested, consequently, that the BSP test, like any test, be carried out under standard

TABLE IV

CASE	PRE-OP. PDR	POST-OP. PDR	POST-OP. INTERVAL	TYPE OF OPERATION
			(Days)	
1	13.0	11.4	9	Lumbodorsal splanchnicectomy
2	14.2	11.3	8	Lumbodorsal splanchnicectomy
3	15.5	13.6	9	Lumbodorsal splanchnicectomy
4	13.2	11.5	8	Lumbodorsal splanchnicectomy
5	9.2	6.9	10	Lumbodorsal splanchnicectomy
6	17.8	13.7	12	Lumbodorsal splanchnicectomy
7	10.9	13.7	8	Lumbodorsal splanchnicectomy
8	12.2	12.6	16	Lumbodorsal splanchnicectomy
9	11.5	12.8	9	Lumbodorsal splanchnicectomy
10	11.5	11.8	11	Lumbodorsal splanchnicectomy
11	10.8	10.9	12	Resection of colon
12	9.5	9.4	10	Cholecystectomy
13	12.3	14.5	8	Transurethral prostatectomy
14	15.5	13.1	6	Appendectomy
15	12.7	9.7	13	Partial gastrectomy
16	12.7	11.7	8	Cholecystectomy

Effects of operation. All tests were performed with the patient supine. No patient was in shock or markedly anemic at the time of testing. Some were receiving mild analgesics or antibiotics.

conditions (i.e. patient fasting and lying down), but that a test need not be discarded merely because the subject was ambulatory or had eaten.

Effect of operations. Table IV presents the results for PDR determined pre- and post-operatively in a number of patients.

Comment. Changes in PDR apparently may occur and persist as long as 10-20 days post-operatively. Since dorso-lumbar sympathectomy appears to reduce hepatic blood flow in the early post-operative period⁹, PDR might be expected to be reduced following this operation in particular. It must be recalled, however, that the pre-operative PDR may be affected by the disease

* Although in the observations cited, (8) removal rate, extraction ratio, and EHBF decreased on tilting, the absolute amount of dye removed from each 100 ml. of plasma increased moderately after tilting in 7 out of 8 control subjects. This also supports the concept of some inverse relationship between blood flow and dye extraction.

for which the patient is being subjected to surgery, and that post-operative PDRs are subject to a barrage of influences, including changes in blood flow as well as changes in hepatic cellular function. Changes in the removal of BSP occur following operations, but they are not necessarily uni-directional nor specific.

Effect of consecutive injections of BSP. Thirty minutes after a single intravenous injection of BSP, a second identical dose was given to 9 subjects. The effect was invariably the same: If PDR was constant following the first

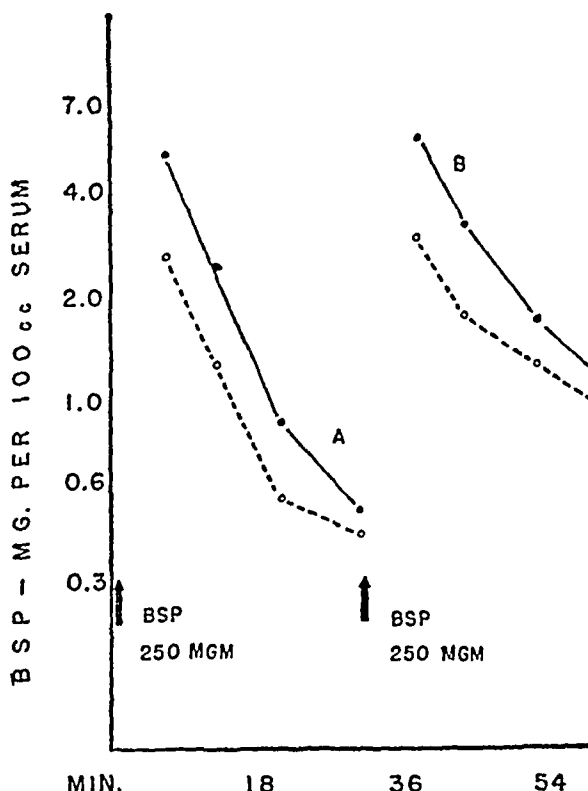


FIGURE 1. Effect of a second identical dose of BSP 30 minutes after the first. Solid lines represent PDR in peripheral venous blood; broken lines represent PDR in hepatic venous blood. Note that PDR at "A" is less than PDR at "B", as discussed in the text.

dose, "saturation" was evident after the second; if some "saturation" was evident after the first dose, it was more pronounced after the second. In patients with impaired hepatic function, the removal of dye could be practically abolished by giving such repeated doses.

In 5 subjects, BSP was determined in hepatic venous blood as well as peripheral venous blood following injections 30 minutes apart. The results of two such tests are plotted in Figure 1 and demonstrate the important point observed in all five: "saturation" was always accompanied by a pronounced reduction of the extraction ratio.

In a normal subject (Table I, S. K.) the PDRs of two doses of BSP given 4 hours apart were identical, but removal of a second dose of BSP by an abnormal liver might be affected by a dye-injection given some hours previously.

Comment. Several mechanisms may be postulated to account for the phenomenon of "saturation": (1) Hepatic blood flow decreases sharply while BSP is being removed from the blood. (2) BSP, taken up by extra-hepatic areas immediately after its injection, re-infuses into the blood as the concentration of the dye falls. (3) Significant re-infusion of BSP takes place by way of the thoracic duct. (4) The capacity of extra-hepatic sites of BSP uptake becomes impaired. (5) The capacity of the liver to remove dye becomes impaired. (6) A combination of any two or more of the above mechanisms.

Simultaneous measurements of the BSP concentrations in peripheral and hepatic venous blood following single injections of the dye show (Figure 1) that "saturation" is always accompanied by an abrupt decrease in the proportion of BSP extracted by the liver, i.e. the extraction ratio decreases. If "saturation" were principally the result of changes in blood flow, of re-infusion from outside the liver, or of impairment of extrahepatic mechanisms, a parallel decrease of PDR would be expected in both peripheral and hepatic venous blood, and the extraction ratio would not change. It follows that "saturation" is produced principally by impairment of hepatic uptake mechanisms.

Impairment of hepatic uptake mechanisms leading to "saturation" apparently occurs under two circumstances: (1) when hepato-biliary functions are deranged by disease¹, and (2) when the normal liver is presented with an excessive load of BSP.* It would seem, therefore, that the appearance of "saturation" indicates that the maximum capacity of the liver to take up dye under the conditions of the moment is being approached. The capacity of the damaged liver, for example, may permit an uptake of only 50% of a standard dose of BSP before manifesting "saturation". A normal liver subjected to two successive doses of BSP, however, may take up 150% of the standard dose before comparable "saturation" is evident.

Unfortunately, "saturation" is not a very satisfactory measure of the liver's capacity to take up and store BSP. In the first place, hepatic cells not only remove the dye from the blood but also excrete it into the bile channels. Until more is known about this rate of excretion, measurements of hepatic capacity to take up BSP are subject to an unknown variable. Secondly, "saturation" is a relative phenomenon that depends on the concentration of BSP in the blood; it cannot be expressed as an absolute amount independent of plasma

* The excessive load must be presented without exceeding the range of BSP plasma concentrations that the liver is usually called upon to handle—i.e., not over 11 mg. per 100 ml. This is accomplished by giving two doses within 30 minutes of each other. Were the double dose given at one injection, the immediate blood levels would be unusually—perhaps dangerously—high, thereby introducing still another factor influencing BSP removal.

dye levels. For example, in Figure 1, PDR at point "A" is 5.7% per minute. After injection of the second dose, plasma dye levels are increased and the removal of BSP is accelerated so that PDR at point "B" is again 9.2% per minute. As the second dose disappears from the blood, however, "saturation" appears earlier and is more marked than after the first dye injection. Apparently the mechanisms that remove BSP from the blood can function indefinitely under ever-increasing loads provided that a sufficient "pressure head" is maintained between the plasma level of BSP and the dye content of the uptake sites. Under such circumstances, however, extra-hepatic removal of BSP may assume significant proportions and BSP removed may or may not indicate hepatic activity.

Although "saturation" is typical of hepatitis and obstructions of the biliary tract, PDR in certain disorders of the liver may be slow but quite constant. This is particularly true of patients with relatively quiescent cirrhosis (little or no jaundice) and with chronic congestive failure¹. The curtailed hepatic

TABLE V

SUBJECT	CONTROL PDR	10-12 MINUTES AFTER INJECTION PDR	"SATURATION"
D. B.	14.2	10.2	0
F. F.	11.9	9.1	0
T. P.	17.2	15.9	0
S. N.	13.0	10.25	Moderate
F. G.	12.0	7.8	Slight

Effect of intravenous sodium dehydrocholate. All tests were carried out on fasting subjects under identical conditions.

blood flow that appears characteristic of both those conditions^{10, 11} may be chiefly responsible for the low PDR. "Saturation" presumably need not occur in either instance because the load of BSP delivered by the limited circulation may not be sufficiently large to overtax the capacity of surviving hepatic cells. In other cases of cirrhosis, particularly those that are jaundiced, both a limited circulation and impaired cellular function may impair BSP removal.

Effect of other substances excreted by the liver. The effect of administering 1.2 grams of sodium dehydrocholate intravenously was determined in five subjects, the results being presented in Table V. PDR was invariably decreased, in two cases with the appearance of moderate "saturation". In two subjects the effects of sodium dehydrocholate were studied by means of the hepatic catheterization technique, the dehydrocholate being given after the injection of BSP. Figure 2 illustrates the striking results that may be obtained: a temporary but complete cessation of BSP removal by the liver.

Rose Bengal in doses of 150 mgm. was given intravenously to three subjects

immediately following the injection of a standard BSP dose. The PDR of BSP was unaffected, but the PDR of Rose Bengal (usually 6-12% per minute) was decreased and marked "saturation" occurred as contrasted with the control tests when Rose Bengal was given alone.

Two normal subjects received bilirubin (3 mg./kg.) intravenously 7 minutes before BSP injection. PDR for BSP was not significantly affected.* Sodium fluorescein given intravenously in doses of 350 mgm. 15 minutes and 1 minute before a dose of BSP did not affect PDR for BSP in the two subjects tested.

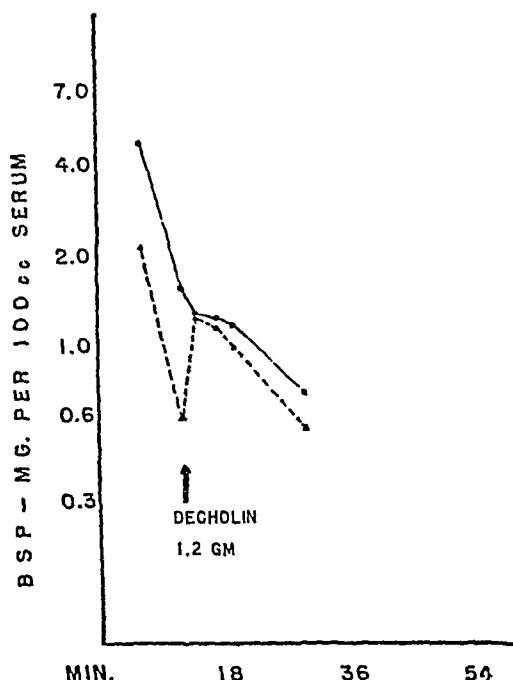


FIGURE 2. Effect of Sodium Dehydrocholate (Decholin) on PDR of Bromsulfalein after standard dose. Solid line represents PDR in peripheral venous blood, broken line represents PDR in hepatic venous blood. The hepatic removal of BSP is nearly abolished for a period of 3 minutes after Decholin injection.

Comment. The studies of Cantarow and Wirts^{12, 13} have shown that the excretion of BSP in the bile is delayed by the administration of sodium dehydrocholate. Our studies indicate that this delay is brought about by an extremely rapid and dramatic blockage of the liver's uptake of BSP. The inhibition of BSP uptake, as indicated by the equalization of dye levels in hepatic and venous blood (Figure 2), and by results obtained with constant infusion techniques¹⁴, is probably not the consequence of changes in total hepatic blood

* The failure of bilirubin in usual dosages to affect BSP removal was studied and confirmed by additional tests using constant infusions of BSP.

flow. A notable feature is the resumption and acceleration of BSP removal following the period of inhibition. In this respect, the effects of dehydrocholic acid and "saturation" differ. Once "saturation" appears, a subsequent increase in PDR, in the absence of further BSP injections, is rarely observed.

Dehydrocholic acid interferes with BSP removal. BSP, in turn, may delay the disappearance of Rose Bengal from the blood, but the disappearance of BSP is little affected by Rose Bengal, bilirubin, and fluorescein. It appears that, at least in the acute experiment, those substances most rapidly removed by the liver may interfere with the uptake of substances removed more slowly, but the converse does not obtain.

TABLE VI

SUBJECT	DOSAGE BSP (<i>mgm</i>)	PDR	"SATURATION"
W. He.	200	7.2	0
	225	6.8	0
F. B.	150	13.7	0
	340	10.5	0
W. Ho.	200	13.0	0
	240	10.1	0
G. C.	220	15.3	0
	330	11.0	0
J. S.	250	14.3	0
	320	10.8	0
M. M.	250	11.1	0
	325	10.0	0
F. I.	150	16.0	0
	300	13.45	0

Effect of altering dosage of BSP. These tests were carried out under standard conditions.

Effect of changing the dose. Table VI shows that PDR may be influenced to some degree by the size of the dose administered.

Comment. Theoretically, an increased dosage of BSP would be expected to overload hepatic removal mechanisms and result in the appearance of "saturation". Actually, however, within the range of doses used (Table VI), the larger dose was not followed by "saturation", but by moderate reduction in overall PDR.

The fact that PDR may be influenced by the size of the dose is consistent with other aspects of BSP removal. If the liver extracted 100% of the dye brought to it, and if hepatic blood flow accounted for $\frac{1}{5}$ of the cardiac output^{2, 11}, the maximum PDR possible would be 20% per minute. Such a PDR is not found normally following the use of standard doses of BSP. As will be reported subsequently¹⁴, however, studies with constant infusions of BSP indicate that

BSP can be removed at rates adequate to yield a PDR of nearly 20, provided that the liver contains little dye. It therefore appears that the amount of dye initially presented to or taken up by the liver affects the PDR, and that its normal range of 10–15% per minute applies only to a specific dose. Presumably the quantity of dye held in the liver may influence PDR long before the hepatic capacity is overtaxed (i.e. before "saturation" appears), but the responsible mechanisms are obscure.

DISCUSSION

Both overloading of the liver with repeated doses of BSP and blockage by sodium dehydrocholate show that changes in the rate at which BSP disappears from the peripheral blood are associated with changes in the amount of dye removed from the blood passing through the liver. The possibility exists that extra-hepatic mechanisms are overloaded with BSP or blocked by dehydrocholic acid concomitantly with hepatic mechanisms, but no evidence exists to indicate that such an assumption is warranted. The direct relationship between PDR and the hepatic extraction ratio, consequently, suggests that the liver is the principal site of BSP uptake following single injections of this dye. A number of reasons have been advanced to show that the R-E system, both within and without the liver, removes BSP, but their validity may be challenged. That the removal of BSP is slightly impaired in dogs for a few days after splenectomy may be ascribed to the decrease in portal blood flow produced by splenectomy, or to the non-specific effects of operation, which impair BSP removal not only immediately after surgery¹⁵, but also in the succeeding 2 weeks (Table IV). The effect of injections of India Ink on BSP removal must also be interpreted with caution. India Ink particles are ingested by Kupffer cells, and, if large, may "jam" the hepatic sinusoids without being ingested. In either case, the engorged Kupffer cells or the aggregates of free particles may prevent adequate exposure of the hepatic polygonal cells to circulating blood. Such a mechanical effect may account for the observation that injections of India Ink may affect carbohydrate metabolism¹⁶, usually considered a polygonal cell function. Finally, Smith¹⁷ has advanced much evidence that India Ink, completely apart from its particulate matter, contains hepato-toxic agents. The effects of splenectomy or India Ink injections on BSP removal, in brief, do not prove that this dye is principally removed by the R-E system. Further evidence excluding the significant participation of the R-E system in the removal of dyes used to test hepatic function has been adduced in this laboratory by fluorescence microscopy¹⁸.

Although the liver appears to be the principal site of BSP removal, other tissues can take up this dye under the proper conditions. For example, BSP disappears slowly from the blood even in the face of complete occlusion of the

common duct. As Cohn¹⁹ has shown, BSP also disappears from the blood of dogs that have been hepatectomized, eviscerated, and nephrectomized, nearly one-half of the injected dose being removed in the course of one hour. This figure is misleading, however. If the removal of BSP in Cohn's hepatectomized dogs is expressed in terms of PDR, it is found to be extremely low: 1-3% per minute. A significant absolute amount of dye is removed in these dogs only because of the high concentrations of dye that persist in the blood. Nevertheless, the fact remains that extra-hepatic mechanisms for the removal of BSP do exist and must be taken into account when liver function is seriously impaired. In face of the rapid removal of BSP by the normal liver, however, extra-hepatic mechanisms function so slowly that their influence is probably negligible.

SUMMARY

The percentage disappearance rate (PDR) of Bromsulfalein following a single intravenous injection of this dye was studied under various conditions. The values for PDR were reproducible on repeated tests, were relatively unaffected by eating, but were at times decreased by strenuous exercise. Operations often, but not invariably, decreased PDR during the first post-operative fortnight.

Two doses of Bromsulfalein injected 30 minutes apart produced "saturation" (i.e. a progressive decrease) of PDR. Simultaneous analysis of peripheral and hepatic venous blood, the latter obtained by the technique of hepatic venous catheterization, suggested that "saturation" was principally caused by an overloading of the hepatic mechanisms that take up Bromsulfalein.

PDR was markedly decreased by injections of sodium dehydrocholate; at times a transient but complete inhibition of hepatic removal of Bromsulfalein was induced by this bile-acid derivative. PDR of Bromsulfalein was unaffected by bilirubin, Rose Bengal or fluorescein. The removal of Rose Bengal, however, was slowed by Bromsulfalein.

PDR for Bromsulfalein was, to a limited extent, affected by the size of the dose, a large dose decreasing, a smaller dose increasing PDR.

These observations suggest that:

1. Within a limited range, an inverse relationship holds between the hepatic blood flow and the amount of BSP extracted from each portion of blood passing through the liver.

2. The PDR of Bromsulfalein is determined by hepato-biliary function and hepatic blood flow. Thus PDR in certain hepatobiliary disorders is characterized by marked "saturation" because hepato-cellular capacity is impaired. In other conditions, PDR is slow but with little "saturation", because hepatic circulation is relatively more limited than is hepato-cellular function.

3. The polygonal cells of the liver constitute the principal site of Bromsulfalein uptake and storage. Extra-hepatic sites of Bromsulfalein removal play a very minor role unless liver function is severely impaired.

NOTE:—In a provocative article, Lewis²⁰ has discussed the concept of "hepatic clearance"; i.e., the proportion of the total circulating fluid volume cleared of various test substances by the liver, expressed as a fraction per hour. PDR for BSP also represents the proportion of total circulating plasma cleared of BSP. Thus a PDR of 12% per minute means that 12% of the total plasma volume is being cleared of BSP per minute.

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THIAMINE DEFICIENCY, PYRUVATE METABOLISM AND ACID SECRETION IN MOUSE STOMACHS IN VITRO¹

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Bull and Gray (1945), Conway and Brady (1947) and others have suggested that pyruvic acid is either the source of the hydrogen ions secreted by the parietal cells or that pyruvic acid metabolism is closely associated with the inorganic acid-secreting mechanism. There have been no critical experiments performed to test these hypotheses although we (Davenport and Jensen, 1949) have studied some aspects of pyruvate metabolism in the excised mouse stomach. We have found that the amount of pyruvate formed or used by the stomach is much less than the quantity of acid secreted and that inhibition of pyruvate metabolism and of acid secretion by arsenite are not proportional. We have also found in unpublished observations that the natural inhibitors of acid secretion, enterogastrone and urogastrone, have no effect upon the pyruvate metabolism of the stomach.

Pyruvate is formed by the stomach, and it is used by at least two processes. About half the pyruvate disappearing is reduced to lactate; the remainder is oxidized by unknown routes (Davenport, 1947). In all other tissues so far studied thiamine in the form of thiamine pyrophosphate is essential for pyruvate oxidation, and there is no reason to believe that the stomach is an exception. Consequently, a study of pyruvate metabolism and acid secretion in thiamine deficient animals should reveal the relation between the two. Although a number of scientists have studied gastric secretion in a variety of animals fed diets presumably deficient in thiamine the adequacy of the diets with respect to other vitamins is open to question, and the results are inconclusive. Shay, Komarov, Greunstein and Fels (1946) produced thiamine deficiency in rats by means of a modern synthetic diet. They found that animals suffering from severe acute deficiency exhibited hypersecretion of gastric juice of normal composition and that in only very advanced stages of deficiency the acidity of the juice decreased. However, these workers did not study the pyruvic acid metabolism of the stomachs of their animals, and they did not demonstrate that the gastric tissue was in fact deficient in thiamine. No conclusions concerning the relation between pyruvate metabolism and acid secretion can be drawn from this or any other work in the literature. Our methods of studying acid secretion in vitro are suited to the solution of the problem, and accordingly the work reported here was undertaken.

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METHODS

Mice of the C₃H strain were used. The stomachs were prepared as previously described (Davenport and Jensen, 1948, 1949). The excised stomachs were emptied of their contents and filled with 0.6 to 1.4 ml. of phosphate-buffered salt solution containing 0.02 M glucose and 1 mg. % carbaminoylcholine. They were placed in weighing bottles containing 2 ml. of the same salt solution. The bottles were placed in small brass bombs in which the partial pressure of oxygen was raised to 3200 mm Hg, for we have found in unpublished experiments that this partial pressure of oxygen not only greatly increases the inorganic acid secretion but permits the acid secretion to be stimulated by carbaminoylcholine. The stomachs were incubated at 38° C. for 120 mins.

At the end of the incubation period the internal fluid was removed from the stomach. Its pH was measured, and the total acid added to it during the incubation period was determined by electrometric titration. The fluid was then analyzed for lactate by the method of Barker and Summerson (1941) and for pyruvate by the method of Straub (1937). The most probable amount of carbonic acid in the fluid was calculated by the method previously described. The inorganic acid secreted was taken to be the difference between the total acid and the sum of the lactic, pyruvic and carbonic acids. In some instances the external fluid was analyzed for pyruvic acid.

As soon as the internal fluid had been removed the stomach was trimmed by our standard method. The forestomach and the stumps of the esophagus and duodenum were removed. The remaining glandular mucosa and muscularis were placed in 3 ml. of phosphate-buffered salt solution containing 5 mM pyruvate per liter and incubated at 38°C. under a partial pressure of oxygen of 3200 mm Hg for 120 min. At the end of this period the dry weight of the stomach was determined and the fluid was analyzed for pyruvate. The amount of pyruvate used by the stomach was calculated.

Fed control mice were given an adequate stock diet ad libitum. Thiamine deficiency was produced by injecting mice subcutaneously with 0.025 mg. of neo-pyrithiamine bromide hydrobromide* twice daily and feeding the following diet: Sucrose, 76 gm., Vitamin-free casein, 18 gm., Salt Mixture, 5 gm., Cod-liver oil, 2 gm., Thiamine, 0.08 mg., Riboflavine, 0.5 mg., Nicotinic acid, 10 mg., Pyridoxine, 0.2 mg., Ca pantothenate, 2 mg., Choline, 150 mg., Inositol, 100 mg., Para-aminobenzoic acid, 100 mg. The salt mixture was that of Hubbell, Mendel and Wakeman (1937). As the result of the small amount of thiamin in the diet the mice continued to maintain their appetite and body weight until deficiency suddenly appeared on about the sixth day (Woolley and White, 1943).

* The neo-pyrithiamine bromide hydrobromide was generously supplied by the Merck Institute for Therapeutic Research through the courtesy of Dr. Gladys A. Emerson.

Groups of control mice were fasted so that their loss of body weight equalled that of the deficient mice.

RESULTS

The results are given in Table I. All figures except the dry weight of the stomachs are in micromoles per 120 min. per stomach. The mean values are accompanied by the standard errors of the mean and in parentheses the numbers of observations.

The first two lines show that fasting reduced the dry weight of the stomach by 20 per cent and the rate of acid secretion by 10 per cent. Very little pyruvate accumulated in the internal fluid of stomachs from control or fasted mice. These observations confirm our previous conclusions based on three indepen-

TABLE I

*Inorganic acid secretion and pyruvate accumulation and disappearance in mouse stomachs in vitro.
Results in micromoles per 120 min. per stomach*

	DRY WEIGHT	INORGANIC ACID SECRETED	PYRUVATE ACCUMULATING		PYRUVATE DISAPPEARING
			Internal fluid	External fluid	
	mg.				
Fed controls	20.3 \pm 0.4 (54)	18.2 \pm 0.7 (55)	0.4 \pm 0.1 (34)	0.6 \pm 0.1 (14)	2.6 \pm 0.1 (29)
Fasted controls	16.4 \pm 0.4 (28)	16.2 \pm 0.4 (28)	0.2 \pm 0.1 (28)	0.5 \pm 0.1 (5)	1.9 \pm 0.2 (23)
Mildly deficient	16.9 \pm 0.4 (21)	11.2 \pm 0.3 (21)	0.4 \pm 0.2 (21)	1.7 \pm 0.1 (11)	1.7 \pm 0.1 (21)
Moderately deficient	15.8 \pm 0.4 (23)	10.9 \pm 0.4 (23)	0.2 \pm 0.1 (23)	1.3 \pm 0.1 (8)	1.0 \pm 0.1 (18)
Severely deficient	14.4 \pm 0.4 (24)	8.8 \pm 0.4 (24)	0.3 \pm 0.1 (24)	1.5 \pm 0.2 (9)	1.2 \pm 0.2 (24)

dent analytical methods that pyruvate may be neglected in calculating the inorganic acid secreted. Likewise only a small quantity of pyruvate accumulated in the external fluid.

The deficient mice were classified according to the severity of deficiency. Mildly deficient mice had minimal neurological signs and a weight loss of about 1 gm. These mice were distinguished from normal mice with difficulty. Moderately deficient mice had ataxia of the hind legs, a tendency to rotate the head, and a weight loss of about 2 to 4 gms. Severely deficient mice had generalized ataxia, and they exhibited spontaneous rolling movements and convulsions. Most of the severely deficient mice were at the point of death when they were used.

Stomachs from all classes of deficient mice secreted less acid than stomachs from either control group. However, the difference between the acid secreted

by the stomachs of the mildly deficient and the severely deficient mice is very small. No more pyruvate accumulated in the internal fluid of the deficient stomachs than in the control stomachs, but about one micromole more pyruvate accumulated in the external fluid of the deficient groups. The stomachs of the deficient mice used slightly less pyruvate than the control stomachs.

There was a very poor correlation between the external signs and the biochemical signs of deficiency. The total amount of pyruvate accumulating can be considered to be a measure of the metabolic lesion produced by thiamin deficiency. When the mice were classified according to the amount of pyruvate accumulating it was found that there was no relation between this variable and either the degree of deficiency judged by objective signs or the amount of acid secreted. In 27 pairs of observations the correlation coefficient between the total pyruvate accumulating and the acid secreted was found to be 0.13 and not significantly different from zero. Likewise there was no relation between the ability of the stomachs to use pyruvate and either the signs of deficiency or the acid secreted. Thirty-four stomachs used more than 1.2 micromoles of pyruvate, and these stomachs came from mice in all three classes of deficiency. These stomachs secreted an average of 10.5 micromoles of inorganic acid. Twelve stomachs using between 0.6 and 1.2 micromoles of pyruvate secreted 11.0 micromoles of inorganic acid, and 17 stomachs using less than 0.6 micromoles of pyruvate secreted 9.4 micromoles of inorganic acid.

DISCUSSION

These data show that thiamine deficiency interferes with the pyruvate metabolism of the stomach and reduces its ability to secrete inorganic acid, but they do not prove that some stage in the metabolism of pyruvate is an essential part of the acid-secreting mechanism. If pyruvate metabolism were indispensable for acid secretion there should be a close parallelism between the degree of deficiency and acid secretion. When the degree of deficiency is judged by any criterion there is a very poor correlation with the reduction in acid secretion. The mildest deficiency reduces acid secretion almost as much as the most severe deficiency. On the other hand, in the presence of the most severe deficiency acid secretion is substantially greater than zero.

A more cogent argument can be drawn from a comparison of the pyruvate metabolism with the acid secretion. One micromole or less of pyruvate appears in the fluid bathing normal stomachs during the incubation period, but more is probably formed and used. In the most deficient stomachs about two micromoles appear, and the extra pyruvate is that which would otherwise be oxidized by a normal stomach. Therefore it is likely that not much more than two micromoles of pyruvate are formed during the incubation period. The same figure can be deduced from the data on pyruvate disappearance. When normal stomachs are bathed in a solution of 5 millimoles of pyruvate per liter between

2 and 3 micromoles disappear in the incubation period. This figure represents the maximum utilization of pyruvate; for the concentration used is higher than that obtaining in the tissue, and the rate of disappearance decreases as the substrate concentration diminishes. In severely deficient stomachs the quantity disappearing is reduced to about one micromole. This quantity can be considered to be the maximum amount of pyruvate which could be metabolized by routes other than those involving thiamine, and it, plus the 2 micromoles appearing in the fluid bathing the stomach, represents the upper limit of pyruvate metabolism in the stomach. Consequently it can be concluded that the turnover of pyruvate in normal or deficient stomachs is within the range of 2 to 4 micromoles in two hours.

This figure refers to the pyruvate turnover of the whole stomach, and the figure for the parietal cells must be much smaller. On the unjustified assumptions that the parietal cells represent a tenth of the metabolizing tissue and that the metabolism of pyruvate is uniform throughout the stomach the pyruvate turnover of the parietal cells is estimated to be less than a micromole in two hours. Nevertheless, the stomachs secrete an average of 18 micromoles of inorganic acid in this period. It is difficult to believe that there can be any stoichiometric relation between pyruvate metabolism and acid secretion unless pyruvate is involved in some cyclic process which has escaped detection.

In order to account for the effect of thiamine deficiency upon acid secretion one must have recourse to the unsatisfactory supposition that any degree of deficiency so damages the cells that they are incapable of secreting acid at their maximum rate.

SUMMARY

1. Thiamine deficiency reduces the ability of excised mouse stomachs to use pyruvate, and it increases the amount of pyruvate appearing in the fluid in which the stomachs are incubated.

2. There is a very poor correlation between the biochemical lesions in the stomach produced by thiamine deficiency and the neurological signs of deficiency.

3. Thiamine deficiency reduces the ability of the stomach to secrete inorganic acid *in vitro* by about half. However, there is no relation between the signs of deficiency, the reduction in the ability to use pyruvate or the increase in pyruvate accumulating, and the impairment of acid secretion.

4. It is deduced that the maximum rate of pyruvate turnover in the mouse stomach is about 2 to 4 micromoles in two hours. This figure is much smaller than the rate of inorganic acid secretion.

5. It is concluded that there is no direct, necessary relation between pyruvate metabolism and inorganic acid secretion.

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Case Reports

JULIAN RUFFIN, M.D.

Durham, N. C., Associate Editor in Charge

GASTRIC ULCER IN THE PRESENCE OF HISTAMINE ACHLORHYDRIA

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Experience does not permit us to accept the thesis that an active duodenal ulcer can exist in the presence of absolute achlorhydria, notwithstanding the claims that have been made by some¹ in this regard. Subacute shallow ulcerations of the gastric mucosa, visible only by gastroscopic examination, were reported in 7 cases by Rodgers and Jones². In these cases achlorhydria followed stimulation by histamine. Palmer and Nutter³ accepted the possibility that such subacute gastric lesions can develop in association with achlorhydria, stating that "apparently acute and subacute ulcers may develop in the stomach in the presence of achlorhydria," but emphasized that "such lesions do not become chronic nor are they of large size." Proof that an active, chronic gastric ulcer can coexist with absolute achlorhydria has not been demonstrated satisfactorily heretofore. Reports which have appeared,^{1, 4, 5} suggesting that this association exists, have not been convincing either because of a lack of satisfactory criteria to prove that achlorhydria existed or because of insufficient information with respect to the characteristics of the ulcer.

We wish to call attention to an instance in which a large, deeply penetrating gastric ulcer and histamine achlorhydria coexisted.

REPORT OF CASE

The patient, a white man 25 years of age, first registered at the Mayo Clinic for a routine general examination in 1940. He had no complaints and was apparently in excellent health. There was no family history of carcinoma, pernicious anemia or of peptic ulcer. As a child he had had diphtheria and otitis media. The tonsils and adenoids had been removed in 1922 when the patient was 7 years of age. Otherwise his health had always been excellent.

The patient was seen again on May 15, 1941, with a chief complaint of severe epigastric pain of three weeks' duration. The pain was periodic, ulcer-like, and usually occurred two or three hours after meals. Occasionally, he was awakened by pain between 3 and 4 a. m. Food and an antacid always gave prompt relief. There was no history of vomiting, hematemesis or melena. He had lost approximately 7 pounds during the previous two weeks.

Physical examination revealed a well-nourished white man, 6 feet, $1\frac{1}{2}$ inches (186.7 cm.) tall, and weighing 180 pounds (81.6 kg). Fingerpoint tenderness was present in the midepigastrium on deep palpation. Abnormalities other than this were not found.

An analysis of the gastric contents, after a modified Ewald test meal, did not reveal free hydrochloric acid. The total acidity was 4 clinical units. The next day an analysis was done, with the use of 0.95 mg. of histamine phosphate administered subcutaneously to stimulate gastric secretion. After the administration of histamine, specimens of the gastric content were obtained at fifteen-minute intervals for a period of two hours. Free hydrochloric acid was not present in any of these specimens and the highest concentration of total acidity in any specimen was 14 clinical units. A roentgenogram of the stomach revealed evidence of a large penetrating ulcer which was sharply circumscribed on the lesser curvature of the stomach just below the angle. On gastroscopic examination the ulcer, which had been reported by the roentgenologist, was visualized. The gastroscopist also noted that the edges of the ulcer were sharply defined and slightly irregular, and that there was considerable edema of the adjacent gastric mucosa. The ulcer was estimated by the gastroscopist to be approximately 2 cm. in diameter. The gastric mucosa was not abnormal in any other respect at this examination, although a comment was made that excessive amounts of mucus in the stomach interfered somewhat with the examination. Urinalysis and blood counts were within normal limits and a roentgenogram of the thorax did not indicate any abnormality. Results of the flocculation test were negative.

The patient was hospitalized and an intensive medical regimen was prescribed. After twenty-seven days of treatment, roentgenoscopic examination of the stomach was carried out but evidence of an abnormality was not present. On gastroscopic examination a few days later, definite ulceration was not found, but the site of the previous ulcer was visualized as an area of mucosal irregularity. The gastric mucosa appeared to be normal in other respects.

The man was dismissed from the hospital as an ambulatory patient and was asked to continue the use of a bland ulcer diet. He returned for roentgenoscopic examination at intervals of one and three months from the date of dismissal from the hospital, and on each occasion the stomach was reported to be normal. During the latter visit, gastroscopic examination was also done. A slight increase in redness of the mucous membrane was reported, and a small amount of secretion was noted between the folds; evidence of gastric ulcer could not be seen. The patient continued to follow a bland diet and remained well except for an occasional episode of mild epigastric distress, which was always promptly relieved by drinking milk.

He returned, as advised, for follow-up examination at intervals of eight and fifteen months from the time the original diagnosis was made, and on each occasion roentgenoscopic examination revealed evidence of a normal stomach and gastroscopic examination revealed mild superficial gastritis only. The final examination was conducted two years after the original diagnosis had been made. On this occasion roentgenoscopic examination revealed that the stomach was again normal. Gastric acids also were checked; 0.95 mg. of histamine phosphate was administered subcutaneously to stimulate gastric secretion, and specimens of gastric content were obtained at fifteen-minute intervals for a period of two hours. Free hydrochloric acid was not present in any of the specimens and the highest concentration of total acidity in any of the specimens was 12 clinical units. Although the patient has not been examined since then, correspondence with him for a subsequent five-year period has indicated that he has remained well.

COMMENT

It is apparent from the favorable course of this patient, during a follow-up period of seven years, that the ulcer in question was benign. Since evidence of tuberculosis or syphilis was not present and since a modified Ewald test meal and administration of histamine on two occasions failed to stimulate the production of free hydrochloric acid, we believe that, in the main, the criteria desired by Palmer and Nutter have been fulfilled. They stated that "before the diagnosis of ulcer with anacidity may be made, the anacidity must be 'histamine proved', and the ulcer must be shown not only to be present, but to be not syphilitic, tuberculous or carcinomatous." Of these perhaps the most difficult criterion to meet is that of anacidity. This is evident by a study of previous reports on this subject and is emphasized by Palmer and Nutter³. They reported 3 cases of chronic gastric ulcer in which repeated estimations of the gastric acidity were made. In each of them histamine sometimes failed to stimulate the production of free hydrochloric acid, whereas subsequent stimulation by histamine resulted in an adequate response of acid. Schiff⁶ recorded a similar observation in which a patient received 799 injections of histamine phosphate in 0.5 mg. doses with detailed gastric analyses over a period of four and one-half years. The response of the patient to the injection of histamine varied with respect to the volume output of gastric juice and the acidity of it. Variations from a normal response, to relative achlorhydria, to an occasional interval of absolute achlorhydria, were noted, the latter being manifest by a diminished quantity of content, a diminished total acidity, and an absence of free hydrochloric acid. Schiff⁶ concluded that the human stomach may temporarily lose its ability, or may exhibit a marked decrease in its ability, to secrete free hydrochloric acid for reasons not definitely known, and that a change in the mucous membrane will not be detectable on gastroscopic examination. Conditions under which Schiff's⁶ study was conducted were care-

fully controlled. In view of his findings, it is obvious that it is impossible to assume that free hydrochloric acid was absent during the genesis of the ulcer, in the case we are reporting, even though histamine anacidity was noted on two occasions during our observation of the patient: once when an active ulcer was demonstrable by roentgenoscopic and gastroscopic examination, and at a later time when the ulcer had entirely healed. Furthermore, in view of these observations, we cannot conclude that stimulation by histamine in our case would have consistently demonstrated absolute achlorhydria, had the test been done more frequently than it was.

In the light of our experience, and the experience of others, as recorded in the literature, it can be said that it is unusual to find an active deeply-penetrating gastric ulcer, possessed with every usual criterion of chronicity, associated with histamine achlorhydria. Moreover, a logical explanation of the association is difficult. Though the gastroscopist did not note associated gastritis during the first and second examinations, a mild superficial gastritis was noted during subsequent examinations. Gastritis, even though mild, must be considered as a factor in the abnormal gastric chemism. It is well recognized that chronic gastritis may cause relative achlorhydria, and, if severe, it may be responsible for absolute achlorhydria. It would be most unusual, we believe, however, for mild superficial gastritis, objectively manifest only by slight reddening of the gastric mucosa and by an increase in mucus, as in our case, to be the entire explanation for histamine achlorhydria.

Estimation of gastric acidity has justly won a secure place in the clinical evaluation of ulceration that involves the duodenum and stomach. We have not seen an instance of active duodenal ulcer in which free hydrochloric acid in some degree could not be demonstrated by stimulation with histamine. The case reported herein calls attention to the fact that a large, deeply penetrating, active benign gastric ulcer can coexist with histamine achlorhydria, but our observations in no way prove that such an ulcer develops in a stomach in which a state of persistent, absolute achlorhydria exists.

SUMMARY

This is a case in which a young man had a large, deeply penetrating benign gastric ulcer associated with histamine achlorhydria. Active medical treatment of the ulcer was followed by prompt and complete healing after twenty-seven days, and at the time of this report there had been no evidence of recurrence in seven years. Unfortunately, it is not known what the gastric acidity was before the ulcer developed. The patient had been examined at the Mayo Clinic one year prior to the development of the ulcer, but at that time his health had been excellent, and no examination of the gastric juice had been made. Symptoms of ulcer had been present for only three weeks before an estima-

tion of the gastric acidity was made, and then no free hydrochloric acid was found, either when a modified Ewald meal was employed or when histamine stimulation was used. After the latter stimulus the highest concentration of total acidity was 14 units. Two years later stimulation with histamine again produced no free acid. The highest concentration of total acidity in the several specimens was 12 units. The fact that the man had remained well for seven years shows that the ulcer was benign. It is unlikely that complete achlorhydria developed in the three weeks in which the symptoms of ulcer were present.

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³ PALMER, W. L. AND NUTTER, P. B.: *Arch. Int. Med.*, 65: 499, 1940.

⁴ CHENEY, GARNETT: *California & West. Med.*, 27: 78, 1927.

⁵ MOUTIER, F., AND COLMENARES, J.: Quoted by PALMER, W. L., AND NUTTER, P. B.³

⁶ SCHIFF, LEON: *Arch. Int. Med.*, 61: 774, 1938.

SENSITIZATION TO BROMSULPHALEIN (PHENOLTETRABROM-PHTHALEIN-DISODIUM SULFONATE)*

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During the past thirty years, various halogenated phthalein compounds have been used in clearance tests to detect impaired liver function, and the dye which is most commonly used is phenoltetrabromphthalein disodium sulfonate (bromsulphalein). Since the introduction of this dye in 1924, as a means of testing liver function¹, local and systemic toxic reactions have been noted and recorded in the literature and commonly recognized. However, a review by us of the literature has failed to reveal any reports of true sensitization to bromsulphalein. It is the purpose of this paper to present observations on three patients who have experienced allergic† responses of varying types and severity during studies in which bromsulphalein tests were performed at intervals of 1-14 days or more.

CASE REPORTS

Case 1.—K. K. a 53 year old white male with advanced Laennec's cirrhosis had been maintained on a constant regimen for 119 days. During this time he had received two series of intravenous infusions of human serum albumin, and numerous abdominal paracenteses had been carried out while in the hospital to relieve ascites. There was no past history of allergic reactions. Bromsulphalein clearance tests (5 mgm./kg.) were done at weekly or biweekly intervals. On the 120th hospital day, about 0.25 cc. of bromsulphalein solution was inadvertently injected paravascularly into the subcutaneous tissue of the right forearm. The patient complained of pain in the area, and within 24 hours developed a kidney shaped, painful, circumscribed inflammatory response approximately 10 x 15 cm. in size in the surface tissues of the flexor surface of the forearm. Elevation, immobilization and local application of heat produced rapid improvement and complete subsidence of the inflammation within four days. One month later, 7.1 cc. of bromsulphalein solution was injected fairly rapidly into the median antecubital vein on the opposite (left) forearm. Thirty to sixty seconds after the injection, the patient experienced nausea, retching, weakness, and severe abdominal cramps. He first flushed and then became pale but there was no sweating. He had tachycardia of

*The opinions expressed in this paper do not necessarily represent the official views of any governmental agency.

†Further studies of the allergic aspects of this reaction have been carried out by Drs. Jerome Sievers and Max Samter of the Dept. of Medicine and the Allergy unit of the University of Illinois College of Medicine.
(American Journal of Allergy—to be published)

110 beats per minute, and the radial pulse was weak. During the next 60 seconds the flexor surface of the right arm and the antecubital space became reddened, painful, and swollen. The distribution of the elevated inflammatory area was of exactly the same shape, size, and position as the first local response which had occurred a month previously, and the pain was of equal intensity. At the same time as the reaction occurred in the right arm, a crop of urticarial wheals ranging in size from one to six cm. in diameter appeared on the patient's abdomen, back, buttocks, and limbs. Lesions did not appear on the head or neck. The patient had moderate conjunctivitis but no engorgement of the mucous membranes of the nares. No evidence of asthma was found on physical examination of the chest, nor did any diarrhea occur. Five minims of a 1:1000 solution of adrenalin were given intramuscularly and 50 mgm. of benadryl orally. The systemic manifestations and the intense pruritus accompanying the urticaria were relieved within 30-40 minutes. Thirteen days later 0.1 cc. of a 1:100 solution of bromsulphalein was injected intradermally into the patient's forearm in the area where the previous inflammatory responses had been noted. A single small urticarial wheal, 1 cm. in diameter developed in the next 15 minutes and disappeared at the end of an hour. In an attempt to demonstrate passive transfer of the sensitivity, 0.1 cc. of the patient's serum was injected intradermally into the forearms of two normal subjects. Bromsulphalein solution (diluted 1:100) was then injected into the same sites 20 minutes and 24 hours later but no reaction occurred in either instance.

Case 2.—S. K. a 25 year old white female was admitted to the hospital with infectious hepatitis. Therapy consisted of a high calorie, high protein diet with supplements of choline, liver extract, and B complex vitamins. No history of allergy was obtained. Intravenous bromsulphalein clearances (5 mgm./kg. of body weight) were performed on the first, second, third, seventh and eighth hospital days, with injections of the dye usually at the same vein site. There was no apparent extravascular infiltration and no untoward reaction to the injections. On the 45th hospital day, 37 days after the last injection, while bromsulphalein was being introduced into the same forearm vein, the patient complained of severe pain along the entire proximal course of the vein. Immediately thereafter, numerous small urticarial wheals 1 cm. in diameter appeared about the site of the needle puncture, but receded without medication in 20 minutes. Within the five hours following this, a widespread inflammatory response developed which involved the entire circumference of the hand and forearm. The vein was red and tender, but there was no epitrochlear or axillary adenitis. Treatment of the arm with moist hot packs, elevation, and immobilization was required for 72 hours.

Case 3.—L. W. a 19 year old colored male was admitted to the hospital for repair of an umbilical hernia. No history of allergy was obtained. Bromsulphalein (5 mgm./kg. of body weight) was injected intravenously on the first and third hospital days without unfavorable reaction. Eight days later, during an injection of bromsulphalein this patient experienced a reaction identical with that described in the pre-

vious patient, consisting of pain along the vein and urticaria about the venipuncture area, both of which persisted for 20 minutes. Shortly afterward, generalized inflammation of the forearm appeared which subsided after 96 hours of local therapy.

DISCUSSION

When aqueous solutions of the various halogenated phthalein compounds were first introduced as agents capable of demonstrating disturbed liver function, they frequently produced local irritation, phlebitis and thrombosis. Unfortunately, after intravenous dye tests, several deaths occurred which were presumably due to thromboses in large vessels². In one fatality, demonstration of the dye within the thrombus stimulated search for a less toxic material, and in 1924 Rosenthal and White introduced bromsulphalein as a safe test of liver function. Subsequent modifications of the original technique have now been developed so the current procedures possess simplicity and almost complete freedom from reactions. Only occasional undersirable toxic reactions to bromsulphalein have been observed but these are apparently rare and without serious consequences. They consist of local and general reactions. The former reaction arises following improper injection of the dye into extravascular or paravascular tissues and this is at times associated with localized signs of inflammation, phlebitis and thrombosis. Generalized toxic reactions also occur such as transient headache, faintness, and chills. Mateer et al reported that such reactions were much more frequent with the 5 mgm. dose than with a dose of 2 mgm./kg. of body weight³. Unger and Shapiro who used the 5 mgm./kg. of body weight dose noted several instances of severe shaking chills and fever following injection of the dye and one of their patients developed peripheral vascular collapse^{4, 5}. The manufacturers of bromsulphalein attributed the systemic reactions to the presence of a calcium salt of bromsulphalein which is more toxic than the sodium salt. The current manufacturing process completely eliminates the undersirable calcium salt.

Even though the literature contains only rare reports of immediate local and generalized reactions to bromsulphalein, it is important to stress the possibility of such reactions and emphasize the necessity for the slow intravenous injection of the dye. In our studies, an injection rate of 5 cc. per minute has been satisfactory. That individuals can develop a true hypersensitivity to bromsulphalein has not been recognized, and we were unable to find a single report of hypersensitivity following a search of the literature, nor have the manufacturers of bromsulphalein any information about such reactions⁶.

The first patient described, K. K. without doubt has become hypersensitive to the dye for he showed a true sensitization response to injections after a latent period. This consisted not only of an anaphylactoid reaction, but of local tissue sensitivity to provocative testing, and suggests the ability of bromsulphalein to act as a hapten antigen.

The two other cases are not so clear cut. However, both patients developed urticarial wheals and extensive local reactions which occurred after a latent period of 37 and 7 days respectively. It should be noted that an unusual technique was employed in carrying out the bromsulphalein tests on these two patients. In them, the physicians were accustomed to perform serial bromsulphalein tests by repeated injection into only one vein, and frequently to use the same site of entry for the needle. It is quite possible that under these circumstances some of the dye was spilled extravascularly and sensitized surrounding tissues.

Our reason for presenting these cases is to call them to the attention of the profession so that patients who have experienced these types of response will be treated with the same precautions as individuals manifesting other types of sensitivity: that is, a patient should be informed of his condition and further tests should not be carried out without desensitization or proper precautions for the management of potentially dangerous allergic manifestations.

CONCLUSIONS

Allergic reactions were observed in three patients following the use of serial bromsulphalein liver function tests. One patient had an alarming anaphylactoid response involving his skin, cardiovascular, and gastrointestinal systems. In the other two patients, the reactions were mild and localized in the arm used for injections.

The reactions suggest that bromsulphalein may act as a hapten antigen, and that when this test is employed serially, proper precautions should be taken to treat anaphylactoid reactions should they occur.

The authors wish to thank Dr. Robert W. Keeton, and Dr. George Lavers of the University of Illinois Research and Educational Hospital for permission to cite two of their cases, S. K., and L. W. And to thank Dr. Robert Kark and Dr. Robert Johnson for their help and advice.

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Editorials

J. ARNOLD BARGEN IS ELECTED PRESIDENT

At the annual meeting of the American Gastroenterological Association, Dr. J. Arnold Bargaen was elected president. This was a happy choice and a fitting reward for years of distinguished service in gastroenterology, and years of faithful service to the Association. Dr. Bargaen was secretary from 1942 to 1947, second vice-president from 1947 to 1948, and first vice-president from 1948 to 1949.

As everyone knows, Dr. Bargaen has made a life-long study of intestinal lesions and especially chronic ulcerative colitis. Because of his great interest in colitis, physicians have sent him cases from all over the world until today his personal knowledge of the disease in all its bizarre forms has become encyclopedic. In many places ulcerative colitis is looked on as Bargaen's disease.

Dr. Bargaen is a tremendous worker, a prolific writer, an effective speaker, a kind, friendly man, a good colleague, and an able therapist who inspires his patients with hope, and lifts them up with his faith and his enthusiasm.

He is professor of medicine in the Mayo Foundation of the University of Minnesota, and head of a section in the Division of Medicine in the Mayo Clinic. He has been honored by election to the Central Society of Clinical Research, the Central Clinical Research Club, Sigma Xi, and many foreign medical associations. In 1945-1946 he was chairman of the section on gastroenterology of the American Medical Association.

He is the author of some 300 medical publications, including *The Management of Colitis* (1935) and *The Modern Management of Colitis* (1943). He was co-author with Rankin and Buie in writing "The Colon, Rectum and Anus" (1932), and he has contributed long articles on the bowel to several encyclopedias such as those of the Oxford University Press, Piersol and Bortz, and Tice.

The members of the American Gastroenterological Association are glad to welcome "J." to the presidency.

A NEW DRUG FOR NAUSEA

In the year 1947, chemists of the Searle Company prepared a drug called Dramamine (β -di-methylaminoethyl benzohydryl ether 8-chlorotheophyllinate)

and sent some to the allergy clinic of the Johns Hopkins University Medical School for investigation. It was hoped it would be helpful in the control of the symptoms of hay fever and urticaria. Fortunately, some of the drug happened



DR. J. ARNOLD BARGEN

to be given to a woman who all her life had suffered much from car sickness. To her surprise the drug relieved, not only an urticaria she had, but her car sickness. For the first time in her life she had no distress on a streetcar.

At a meeting of the Johns Hopkins Medical Society, in February 1949, Leslie N. Gay and Paul E. Carliner reported on the use of the new drug. Recently in the April 8, 1949, number of *Science* (pp. 359-360) they tell how the giving of 100 mg. of Dramamine every five hours to persons at sea kept 372 of 389 persons from developing seasickness. Placebos were given to a control group in order to rule out a psychic effect.

The tests carried out by Stricklin and Hahn (reported in the same number of *Science*) on air sickness were more strenuous. Men were sent aloft in planes which were then made to yaw, fishtail, roll and pitch until 55.6 per cent of the men who received a placebo got sick. Of those who got Dramamine only 28.7 per cent got sick.

Already a few reports indicate that the drug can be useful in cases of nausea due to nervousness, migraine, fatigue or cerebral arteriosclerosis.

[W. C. A.]

THE CALMING EFFECT OF DIBENAMINE

In a recent number of *Gastroenterology* we have had occasion to comment on the remarkable effects of the drug, dibenamine, which blocks sympathetic action. In a recent article, Dr. F. V. Rockwell (Psychosomatic Medicine, 10:230 [July-Aug.] 1948) reported some interesting results from the use of this drug in persons with certain psychopathologic syndromes. He remarked that dibenamine is moderately toxic, but if properly used it can be safely administered over prolonged periods of time. Rats, given three times the blocking dose daily for two months, showed no permanent ill-effects. Unfortunately, the drug cannot be injected into tissues because it produces necrosis. It can be given safely only by mouth or intravenously.

Rockwell gave 16 neuropsychiatric patients intravenous doses of from 200 to 400 mg. in 500 cc. of a 5 per cent solution of glucose. He ran the dose in during a period of 60 to 90 minutes. Of these patients, 7 had no toxic symptoms, 3 suffered nausea, with or without vomiting, 1 had nausea and mild epileptoid symptoms, and 5 showed epileptoid symptoms of varying degrees without nausea or vomiting. Apparently, dibenamine has convulsive properties, with a selective action on the temporal lobe. One patient started with loud, uncontrollable laughter, and ended up screaming. She said she was experiencing marked fear, and felt she was losing her mind. The patient had previously been feeling dazed, dizzy and miserable, tense and anxious and sometimes depressed and hopeless. Her unhappy reaction to the drug lasted about an hour.

To the internist, the most interesting result was obtained in the case of a woman who for some time had been anxious, depressed, at times alcoholic. She reported that she immediately felt relaxed, with a feeling of tranquility which

was novel to her and for which she was most grateful. Important also was the release from a stomach-ache, which she had had for a long time. The patient also said that immediately her feeling of wasteful nervous energy was greatly reduced, and her power of concentration was therefore doubled. She was able to read well again for the first time in years.

In all, 50 patients were treated, and in some of them the improvement was marked. In others, the drug did not help much. Probably the most important point is that a drug that blocks sympathetic nerves has been found, and one which in some patient can bring tranquility and peace of mind. Perhaps with time other and more satisfactory drugs of this type will be found. A new and important book on the subject is Bovet and Bovet-Nitti's *Structure et activité pharmacodynamique des médicaments du système nerveux végétatif*, published by S. Karger, Basel, in 1948 (849 pp.)

[W. C. A.]

GENES AS DETERMINERS OF CELLULAR BIOCHEMISTRY

David M. Bonner, of Yale University, in the December 31, 1948, number of *Science*, has written an article which will be of tremendous interest to all nutritionists and biochemists. He there sums up some of the work which has been done of late particularly with the bread mold, *Neurospora*. As many readers of *Gastroenterology* know, when this bread mold is exposed to radiation of certain types, mutants appear which apparently have lost one gene, and with this change have lost the ability to form an enzyme which will bring about a certain biochemical reaction. As a result, in order to grow the new strain of *Neurospora*, the experimenter must add some chemical to the medium. In this way the intermediate products of a number of chemical reactions in the body have become known.

Incidentally, it is curious that the mutants rarely develop an ability to perform new reactions. Usually they lose the power to perform some old reaction. Already it is known that the mutant strains of *Neurospora* have lost their ability to synthesize the B vitamins, most of the amino acids, and several of the purines and pyrimidines.

Evidence has been obtained to indicate that at least four separate genes are essential to the synthesis of niacin. Alteration of any one of these four genes gives rise to a mutant which cannot grow unless niacin is added to the culture. In general, it has been observed that several genes are concerned with the synthesis of each of the vitamins and amino acids.

Very interesting is the fact that the general pattern of synthesis is similar for *Neurospora* and the higher plants and animals. Significant also is the fact that in a mutant which lacks the enzyme to produce a certain chemical reaction

this substance, because it cannot be broken down and metabolized, accumulates in the tissues and there may do harm, much as in a gouty person where uric acid accumulates in the body until it does harm.

Nearly every biochemical reaction that occurs in a living cell requires enzymatic catalysis. Since a gene is necessary for the production of each one of these enzymes, the question is now being raised, "Will not a cell need an astronomical number of genes in order to carry out all the various reactions that are necessary to its metabolism?" Today the geneticists estimate that the number of genes in various organisms is around 10,000; hence the question is, "Are 10,000 enough to run a cell?" Bonner thinks they probably are. The number of necessary reactions which are now known to biochemists runs to about 1,000, which leaves 9,000 for the working of other unknown types of reaction. Possibly this is enough, although it would seem doubtful.

One question that is coming up in the field of human genetics is, "Are neuroses and psychoses and convulsive disorders each produced by one defective gene?" From the fact that a defective nervous inheritance shows itself usually in so many different ways in the various members of a family, it seems probable that it takes at least hundreds of good genes to make a good brain, and perhaps scores of bad genes to make a very poor brain. Future research will tell if this view is correct. Some day, also, we may know how many genes it takes to make a tendency toward duodenal ulcer, or congenital polyposis of the colon.

[W. C. A.]

Comments

Readers are invited to contribute to the Comment Section of Gastroenterology short notes expressing their opinions on controversial topics and matters of current general interest.

GASTROSCOPY UNDER PENTOTHAL-CURARE ANESTHESIA

Since our paper on the subject appeared in GASTROENTEROLOGY (10: 978, 1948), additional experience with gastroscopy under pentothal-curare anesthesia has demonstrated the advisability of using intratracheal intubation for a constant supply of oxygen in the strength of 25% to 50% diluted in nitrous oxide. This is an additional safeguard which is indicated.

We have encountered no difficulty with instrumentation with the intratracheal tube in place.

It is to be again emphasized that this procedure is not to be used routinely, but only in the most difficult cases and only if a competent anesthetist is in charge of the anesthesia.

S. J. STEMPIEN, M. D.

Book Reviews

THANK GOD FOR MY HEART ATTACK. *Charles Yale Harrison*. Henry Holt and Company, Inc. New York. 1949. pp. 144. Price \$2.50

This is the story of a writer who suffered an acute coronary infarction and came out of it alive. Being a writer of ability he is able to describe well his emotions and his experiences from the start of his pain to the time when he was able to go back to work. He has done a good job and the book should be read by physicians. All such books should be read by physicians to show them how a patient reacts to what they say and do. There are many things we physicians would not do to patients if we read more of the books of this type that have been written in the last fifty years.

MEDICAMENTS DU SYSTEME NERVEUX VEGETATIF. *D. Borel et F. Borel-Nelli*. Bale (Suisse) S. Karger, pp. 849.

This is a splendid work which every library and every department of pharmacology and physiology and research medicine will have to have. It deals with scores or hundreds of synthetic substances which have effects on the vegetative nervous system. It is a veritable mine of information.

PSYCHOSOCIAL MEDICINE. A STUDY OF THE SICK SOCIETY. *James L. Halliday, M.D.* W. W. Norton & Company, Inc. New York. pp. 278. Price \$3.50.

Dr. Halliday of Scotland is a prominent British psychiatrist now greatly interested in public health. He has been a general practitioner and epidemiologist and a public health administrator. Recently he was the guest in this country of the Rockefeller Foundation.

When a thoughtful, devoted physician takes over the job of caring for the health of a nation, he begins to think of disease, not as something that affects an individual for a week or two but as something that affects millions of persons to different degrees. He begins to wonder why certain persons get the illnesses they do and what could be done to protect them from trouble; what could be done to protect society from the tremendous burden of the care of the chronically ill. The doctor begins to see also very clearly that his biggest problem is that of caring for psychopathic persons and persons who have become ill because of the strains of life. The doctor begins to study disease not only in the twenty minutes in which a patient is in the office but throughout the man's lifetime. He begins to see the relation between early rheumatic fever and chorea and later heart disease, hypertension, kidney disease, anemia, etc. The doctor begins to see also how a tendency to fibrositis or arthritis can dog a man's footsteps from the age of twenty to the age of eighty. He gets interested also in the way in which a tendency to disease shows up in the several brothers and sisters in a large family.

To the philosophically inclined physician this can be a most interesting book to read. The book shows perhaps better than any other such treatise why civilized man is now making fumbling attempts at improving the health of the nation as a whole. Society may not as yet be going at this sensibly, but eventually it may muddle through to the sort of medicine which Dr. Halliday sees way off in the future.

FOOD AND FACTS FOR THE DIABETIC. *Joseph H. Barach, M.D.* Oxford University Press, New York. 1949. pp. 113. Price \$4.00

This is an attractive volume. Most of it is taken up with diet lists, some for men and some for women. It looks like a valuable and helpful volume for diabetics. The author says that diabetes appears to have been known in 1500 B.C. It was described in an Egyptian manuscript.

HOW TO BECOME A DOCTOR. *George R. Moon, A.B., M.A.* The Blakiston Company, Philadelphia. 1949. pp. 131. Price \$2.00

This is a helpful volume for anyone planning to go into medicine, because it answers practically all the questions that such a person would be asking. It deals with the problems of choosing a college and gives a list of the schools with their minimum admission requirements and the average annual fee for instruction. Apparently that fee now runs anywhere from \$200 for state residents to perhaps \$750 for private schools or non-resident in state schools. There is information also about schools for veterinary medicine and chiropody.

It is a book that ought to be in every library.

SCHISTOSOMIASIS MANSONI NO BRASIL. *Drs. Cesar Pinto e Antonio Firmato de Almeida.* 1948. Imprensa Nacional, Rio de Janeiro, Brasil. pp. 287.

This is a large monograph with 287 pages beautifully printed and written and illustrated, on *Schistosoma mansoni*, as it is met with in Brazil. The writers have done a fine piece of work. In some of the provinces of Brazil over 30% of the samples of feces examined contained *Schistosoma*, and about 15% of the livers examined were infested. The authors have found that the armadillos of Brazil are highly susceptible to infestation. The authors show the picture of a woman with a spleen which must have weighed about half the weight of the person.

This volume will be of interest to all students of tropical medicine.

INTERNATIONAL SOCIETY OF INTERNAL MEDICINE

The International Society of Internal Medicine will hold its second meeting in Paris in the spring of 1950. This organization was founded as a result of the efforts of a group of Swedish and Swiss physicians with the approval and assistance of UNESCO. An organization meeting, held in Basle in September, 1948, was attended by physicians from sixteen countries. Many of the founders' group (nearly all of whom are teachers of medicine in their respective countries) have travelled or studied in the United States. The organization is a member of the Association of International Medical Congresses, which met under the auspices of WHO and UNESCO in Brussels in April, 1949.

The purpose of the International Society of Internal Medicine, as stated in its constitution, is "to contribute to the development of scientific knowledge and education in internal medicine and to promote personal relationship between internists in all countries." It is obvious that such an organization may do much to re-establish the international contacts between practitioners and teachers of internal medicine which were disrupted by World War II, and for this reason, may appeal to many American physicians.

Membership is restricted to qualified internists, who have been accepted as members of the national associations of internal medicine in their several countries. Dues are purely nominal (10 Swiss francs per annum). A substantial group of Swiss, Italian and Swedish physicians have already applied for membership, and plans for the Paris congress are proceeding under the direction of Professor A. Gigon of Basle (President of the Society), Dr. Nanna Svartz of Stockholm and Dr. L. Justin-Besancon of Paris.

American, Canadian and Latin-American physicians who may be interested in membership may direct their inquiries to Dr. A. M. Snell, 102-110 Second Avenue Southwest, Rochester, Minnesota.

ABSTRACTS OF CURRENT LITERATURE

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MOUTH AND ESOPHAGUS

SWEET, R. H. Carcinoma of the superior mediastinal segment of the esophagus. A technique for resection with restoration of continuity of the alimentary canal. *Surgery*, 24: 929 (Dec.) 1948.

A lesion in the superior mediastinal segment of the esophagus is too high for the performance of a supra-aortic intrathoracic esophagogastric anastomosis. A technique is described whereby the stomach may be brought up behind the hilum of the lung and lateral to the aortic arch. The gastric fundus can be placed in the apex of the left pleural cavity.

Through a transthoracic approach (removing the eighth rib), the stomach is mobilized by incising the entire gastrocolic ligament to the level of the pylorus. The left gastric vessels are cut and the gastrohepatic ligament is incised to the level of the pylorus. Blood supply to the stomach is maintained through the right gastric and right gastroepiploic arteries. The second stage of the operation involves removal, through an anterior incision, of the medial half of the left clavicle and a corresponding segment of the left first

rib. This produces an opening in the base of the neck through which the fundus can be drawn, without danger of compression, for anastomosis to the high-lying proximal esophageal segment.

A case is reported wherein this operation was applied successfully to a 55-year old man who had an esophageal carcinoma at the level of the manubrium of the sternum. The operation affords restoration of the continuity of the alimentary canal in place of resorting to a gastrostomy or a cervical esophageal stoma. For anatomic reasons, the operation does not permit wide dissection and would not be indicated in a patient where there is appreciable local invasion of structures surrounding the upper esophagus by the neoplasm.

LEMUEL C. MCGEE.

STOMACH

FINESTONE, E. O. The fallacy of hydrochloric acid interpretations in gastric surgery. *N. Y. State J. Med.*, 48: 2724 (Dec.) 1948.

The operations performed in the surgical treatment of peptic ulcer are aimed at the

reduction of the gastric acidity. Failure to examine the postoperative gastric contents for total chlorides has led to some misconceptions in interpreting the results of surgery. Hydrochloric acid is the major constituent of gastric secretion and is formed mainly in the fundus and body, and to a lesser extent in the pyloric region. Its main function is to activate pepsin. The total chlorides include those derived from free HCl, combined HCl and inorganic chlorides. The last are either secreted as such by the gastric mucosa, or result from the combination of free HCl (in the gastric juice) with regurgitated duodenal or jejunal contents. The concentration of free HCl in the stomach will depend on many factors. The total chlorides are the truest indication of the total HCl secreted.

PHILIP LEVITSKY.

KRISNAPOLLER, N. H. Beitrag zum Reliefbild beim Magencarcinom [Mucosal relief studies in gastric carcinoma]. *Acta Radiol.*, 28: 352 (Aug.) 1947

The importance of mucosal relief studies in the early diagnosis of gastric carcinoma has been repeatedly stressed. Characteristically, the mucosal folds are indurated, stop suddenly at the tumor margin, and ulcerate in a rather typical saucer-like fashion. Where infiltrating carcinoma invades the mucosa as well as the submucosa, the rugae are not easily obliterated by palpation, whereas those tumors that are limited to the submucosa will exhibit an obliteration of the rugal folds on fluoroscopic palpation. Another source of error concerns the fact that, on X-ray examination, superimposition of the gastrointestinal folds of one wall onto a lesion on the opposite wall may so mask the pathological changes that an ulceration may be considered benign instead of malignant or even completely absent. Films taken in various obliquities as well as careful pressure fluoroscopy will reduce the incidence of errors.

A. I. FRIEDMAN.

OVERGAARD, K. Polyps of the stomach and duodenum. *Acta Radiol.*, 30: 343 (Nov.) 1948.

Twelve gastric and 5 duodenal polyps were observed by the author over a period of 11 years. Gastric polyps are most commonly

found in the antrum, in patients over 40 years of age. The incidence of both types varies from 0.1 to 2.3 per cent. Except for leiomyomata, polyps are the most common benign tumor in these organs. The most recent studies indicate that they result from an extreme inflammatory reaction. Histologically, they are composed of various types of epithelial cells on a connective tissue stalk, not specifically glandular epithelium.

The symptomatology is indefinite and includes dyspepsia, postprandial distress, frequent hematemesis or melena, occasional nausea, vomiting of mucus, and rarely, colicky pain. Diagnosis is by X-ray. In the stomach, the filling defect generally is central and rounded, circumscribed, occasionally lobulated. The stomach contour is normal and mobile, the mucosa is normal, as is peristalsis. Compression is necessary to find small polyps. With large polyps, the picture is blurred and the filling defect not characteristic. The most favorable technique is sparse barium-filling with mild compression in the horizontal position.

Although bleeding is an occasional serious symptom, it is never menacing. The principal complication is malignancy, and its incidence varies from 2 to 40 per cent. Only 1 of the 17 cases presented had cancer in the same stomach. The frequency of cancer of the stomach where polyps already exist is 4-5 times as high as cancer of stomach without polyps. However, it is likely that the irregular wart-like mucosal thickenings, that are a constant feature of chronic atrophic-hypertrophic gastritis, give rise both to polyps and cancer. While the polyp must be considered as a sign of the presence of a pathologic condition which may develop into cancer, it is not in itself a pre-cancerous condition which calls for radical therapy. Treatment therefore is dietetic, with constant observation—including gastroscopy.

Follow-up studies have shown increase, decrease, no change in size of polyps, or a rare malignant growth. For differential diagnosis, myomata, fibromata and neurinomata have a broader base, a smooth outline that does not change with pressure, and often a central crater. A prolapsing hyperplastic antral mucosa may make the diagnosis difficult.

A. I. FRIEDMAN.

COVE, A. M. AND CURPHEY, W. C. Prolapse of redundant gastric mucosa. *Surg. Gyn. Obs.*, 88: 108 (Jan.) 1949.

A review of 650 consecutive X-ray examinations revealed that prolapse of redundant gastric mucosa occurred in 22 cases (3.38%) indicating that the condition is more common than generally suspected. The symptoms of prolapsed mucosa are never characteristic and do not permit a clinical diagnosis of the disorder. Consequently, diagnosis is based on the roentgenologic findings which show a central filling defect near the base of the bulb, most often lobulated. The most common complication of prolapse is gastrointestinal hemorrhage. Treatment in these patients is usually confined to medical measures. Surgery, however, is indicated in those cases who do not respond to medical treatment and in those patients having repeated severe gastrointestinal hemorrhage. The surgical procedure of choice has been antrotyomy with division of the pyloric muscle, resection of an abundant portion of the prolapsing gastric mucosa, followed by a Horsley or a Finney pyloroplasty. The authors do not feel justified in doing the more radical procedure of partial gastric resection.

FRANCIS D. MURPHY.

BOWEL

JONES T. E. AND TURNBULL, R. B. Familial polyposis of the colon: diagnosis and treatment. *Surg. Clinics N. Am.*, 1171 (Oct.) 1948.

The authors report a series of 22 cases, in 8 of which carcinoma was present at the time of first examination. There was usually a history of bloody diarrhea, loss of weight and anemia. Diagnosis was made by proctoscopic examination; the double air contrast enema technic being especially valuable. Family history in 9 of the 22 cases revealed polyposis in other members of the family.

The recommended treatment is surgical and, because of eventual malignant degeneration, radical procedures are advocated. The ideal procedure is obliteration of the polyps from the anus to the lower 5 inches of sigmoid colon, followed by ileosigmoidostomy; and, at a still later date, colectomy. The objective is removal of all potential neoplastic tissue except that which can be viewed

through the proctoscope. The technic and preparation of such cases for operation is described. Four cases, illustrating important features of the disease, are presented. It is believed that all such polyps will ultimately undergo malignant change, but the time of such change is uncertain.

FRANK G. VAL DEZ.

MAXWELL, E. A., CRILE, G. JR., AND DINSMORE, R. S. Malignant tumors of the small intestine. *Surg. Clinics N. Am.*, 1149 (Oct.) 1948.

Forty cases of malignant tumors of the small intestine are reviewed, carcinoma being present in 21, sarcoma in 13, carcinoid in 5, and sarcoma plus carcinoid in 1. Malignant tumors of the small intestine form only 3 per cent of such tumors found in the intestinal tract. An equal frequency was found in the portions of the small intestine but carcinoma was more frequent in the duodenum and jejunum, whereas sarcoma was more frequent in the ileum. The average age of patients with malignancy of the small bowel is 52.6 years.

The symptoms usually appear late in the disease and include loss of weight, fatigue, anemia, and cramping pains in the mid-abdomen. A diagnosis was made by roentgenography in 46 per cent of cases. The technic was found to be more reliable if only small amounts of barium were given by mouth. When the lesion was low, a barium enema afforded better visualization of the terminal ileum.

The treatment of choice in the early stage is resection with side-to-side anastomosis. Palliative procedures such as gastroenterostomy or enteroenterostomy may be preferable in more advanced cases. Postoperative X-ray therapy is indicated in the cases of sarcoma. The prognosis is poor except in the carcinoid tumors.

Three case reports are given; one of carcinoma, one of sarcoma and one of coexisting sarcoma and carcinoid in the terminal ileum.

FRANK G. VAL DEZ.

HASKELL, B. AND FRIEDMAN, M. H. F. One year's treatment of non-specific ulcerative colitis with intestinal extract. *Am. J. Surg.*, 709 (Dec.) 1948.

Believing non-specific ulcerative colitis to be an intestinal deficiency disease involving an intrinsic protective factor, extracts of hog intestinal mucosa were therapeutically administered to 27 patients for a minimum period of 1 year. Included in this series, were 8 men and 19 women, whose ages ranged from 16 to 57 years. Diagnosis of each case was established after clinical, laboratory, roentgenologic and endoscopic studies and similar examinations were used in determining the results of treatment. The extract of hog intestinal mucosa was administered in divided doses of 50-100 gm. daily. Treatment continued for several months at this dosage level and was reduced or withdrawn when improvement was marked. Symptomatic and sigmoidoscopic evidences of improvement were noted in 24 cases. After remission of symptoms, withdrawal of the intestinal extract or substitution of a placebo resulted in relapse, with remission occurring again upon resumption of treatment. It is probable that sustained improvement can be maintained only by continued administration of the extract.

MICHAEL W. SHUTKIN.

BACON, H. E. AND VAUGHAN, G. D. Surgical management of lesions of the large bowel
Am. J. Surg., 76: 648 (Dec.) 1948.

In the authors' series of 800 patients with cancer of the colon, the distribution was as follows: Sigmoid, 112; rectosigmoid, 261; rectum, 206; and anal canal, 21. The approach to the management of malignancy of the lower colon included: (1) All growths involving the mid and proximal sigmoid were removed by immediate establishment of intestinal continuity either by the open or closed technique, or the Mikulicz-Rankin method of exteriorization. (2) All lesions involving the distal sigmoid, rectosigmoid and ampullary portion of the rectum were extirpated by proctosigmoidectomy without colostomy and with preservation of both the internal and external sphincters. (3) Those lesions involving the anal canal and lowest 3 cm. of the rectum were excised by methods in which the sphincter muscles are sacrificed and a permanent abdominal colostomy established. The incidence of local recurrence was 17.9 per cent. Benign polypoid lesions of the sigmoid were removed through a sig-

moidotomy; in 50.9 per cent the lesions were found on serial section to be grade I or grade II adenocarcinoma.

In chronic ulcerative colitis, surgery must be considered a means of preserving life after the failure of a thorough rigid medical regimen. Diverticulitis is generally a medical problem with surgery reserved for the complications such as abscess, perforation, obstruction, and suspected malignancy. Closure of a colostomy proximal to the lesion is best postponed for several months. Hemicolectomy and proctosigmoidectomy, with transplantation of the transverse colon to the anus and preservation of the anal sphincter musculature, were performed in a series including polyposis, diverticulitis, malignancy, ulcerative colitis with malignancy, and stricture. The most satisfactory treatment for rectal stricture due to lymphogranuloma venereum is colostomy followed later by perineal excision. In intestinal polyposis, radical surgical extirpation should be instituted with no delay.

MICHAEL W. SHUTKIN.

SCARBOROUGH, R. A. AND KLEIN, R. R. Polypoid lesions of the colon and rectum
Am. J. Surg., 76: 723 (Dec.) 1948.

Observations are reported on 458 cases of benign polypoid disease of the colon and rectum. Benign non-premalignant tumors encountered were fibroma, myoma, endometrioma, hemangioma, granuloma, lymphoid polyps, and giant follicle lymphoid tumors. Premalignant types, comprising 95 per cent of cases, were inflammatory hyperplasia, hyperplasia, adenoma and papillary adenoma. Malignant degeneration was found in 30 per cent; in only 8 cases, was it possible to demonstrate this by multiple biopsies. Of the 18 malignancies, 2 were inoperable and 14 were treated by radical resection. Every presumably benign papillary adenoma should be completely excised or removed by diathermy snare, and all of the tumor carefully studied histologically for malignant degeneration.

The incidence of polyps in males was 10 per cent greater than in females. The ages ranged from 5 days to 94 years. The infrequency of diagnosis of polypoid disease in the second decade of life is striking. Diagnosis was reached by endoscopic and roentgen examination which was advised annually

in all treated cases. X-ray diagnosis must include both the barium enema and double contrast air examination of the colon and rectum. Bleeding in the presence of diverticulitis has usually been found due to a co-existing adenomatous neoplasm. Proper treatment is dependent upon accurate determination of the presence or absence of malignancy. Methods of treatment range from rigid wire diathermy, diathermy snare, electrodesiccation, colostomy to resection.

MICHAEL W. SHUTKIN.

KERR, J. G. Polyposis of the colon in children. *Am. J. Surg.*, 76: 667 (Dec.) 1948. Bleeding from the bowel in children is most often due to an adenomatous polyp of the rectum or colon. The two clinical types of intestinal polyposoid disease are multiple polyposis of the familial type and polyposoid lesions, in which one or very few polyps are found.

In a consecutive series of 349 children, polyps were discovered in 100. The single symptom common to all was the painless passage of blood-streaked mucus from the bowel. The history of bleeding covered periods from a few days to several years. The passage of small blood clots was frequent. Larger hemorrhages were caused by the sloughing of large portions of the polyp; self-amputation occurs frequently in children. In 68 patients the polyp was single, and in 32, there were multiple polyps. Ninety-eight cases were 11 years of age or younger; the average age was 3.4 years. Other than the passage of bloody mucus, symptoms (in the order of frequency) were: protrusion of the polyp (28%), diarrhea (19%), and abdominal cramps (18%). Rectal prolapse is differentiated from protrusion of a polyp by the history and the dark port wine color of the protruded polyp.

True diarrhea is not uncommon. Cramps vary in intensity with the size and location of the polyp. The diagnosis depends upon an adequate endoscopic and radiographic examination of the colon. The complications of severe bleeding, anemia, obstruction, intussusception and carcinoma are serious indications for early extirpation. Electrocoagulation is adaptable for terminal lesions, whereas colostomy is performed for the higher tumors. These polyps appear to be true neoplasms and are subject to malignant degeneration

in children, although not with the same frequency as observed in adults.

MICHAEL W. SHUTKIN.

ALEXANDER, M. B. Infantile diarrhoea and vomiting. A review of 456 infants treated in a hospital unit for enteritis. *Brit. Med. J.*, 4587: 973 (Dec.) 1948.

The organization of a hospital unit for the treatment of enteritis in infants is described. A total of 456 infants under the age of 1 year was treated in this unit during 1945 and 1946. Two hundred and fifty-eight of the series (56.6%) were dehydrated during the course of their illness. There were 22 deaths, a mortality rate of 4.8 per cent for all cases, or 8.5 per cent for infants who were dehydrated. There were no deaths among infants who were not dehydrated. Parenteral infections were found on admission in 238 cases. The association between parenteral infections and dehydration is low, and this series does not support the view that such infections are a major factor in the causation of diarrhea and vomiting. The importance of prevention or early correction of dehydration, the necessity for intravenous therapy in severe cases, and the need for prevention of cross-infection are emphasized. This implies that the provision of adequate facilities and a staff of physicians and nurses, experienced in the technique of barrier nursing and the treatment of dehydration in infants, is essential. It is suggested that these requirements are best fulfilled by the establishment of self-contained hospital units for the treatment of enteritis.

JOSEPH B. KIRSNER.

JOHANSON, C. Einiges über den Mechanismus bei der Entstehung bzw. Reposition von Caecum und Sigmoidumvolvulus. [Comments on the mechanism of the cause and reduction of volvulus of cecum and sigmoid.] *Acta Radiol.*, 28: 209 (June) 1947. The distribution of volvulus location is stated to be approximately, sigmoid-50%, small intestine-30%, and cecum-20%.

One of the chief factors is the mobility of the bowel segment as demonstrated by the length of the mesentery. Another factor is the spatial relationship of the various viscera in the abdomen. Rotation of up to 180 degrees (physiological volvulus) may oc-

cur without clinical symptoms. When volvulus does occur, its behavior will vary with the degree of laxity of the abdominal walls, the distension of adjacent loops of the small bowel or colon, and the presence or absence of other mechanical factors such as adhesions and tumors. Occasionally, a volvulus may be reduced by means of a barium enema, aided by decompression of the distal bowel by means of a rectal tube.

Two cases are presented. A woman, 36 years of age, with a sudden onset of para-umbilical pain, revealed, on a scout film, a greatly distended cecum that had folded itself on the ascending colon and extended up to the rib margin (kinktorsion). A barium enema filled the colon, but produced pain when the contrast material reached the cecum. A postevacuation film revealed that the cecal volvulus had been reduced. A 77-year old female entered the hospital with ileus after one week of vomiting. No hernias were obvious. Barium enema demonstrated a rotated sigmoid loop and a narrowing of the lumen between the sigmoid and descending colon. At operation, a distended and tense loop of small bowel was drawn across sigmoid at the point of volvulus into the femoral hernia pouch. This loop mechanically compressed both arms of the sigmoid at the point of torsion. Undoubtedly, the volvulus was secondary to the incarceration of the small bowel.

A. I. FRIEDMAN.

PENBERTHY, G. C. AND BENSON, C. D. The complications of Meckel's diverticulum in infants and children. *Surg. Clinics N. Am.* 1221 (Oct.) 1948.

Five important complications of Meckel's diverticulum are discussed. Discharge of yellowish brown fluid from the umbilicus may occur in cases where the diverticulum has not detached from the umbilicus. Treatment is removal of the diverticulum. Inflammation with or without perforation is more common in children than adults. Appendicitis is the usual preoperative diagnosis. Barium studies rarely reveal an abnormality. This condition should be searched for especially when the appendix does not explain the symptoms. Diverticulectomy or resection of the ileum should be done depending on the individual

lesion found. Another complication, hemorrhage, may occur as an acute massive episode or recurrent mild bleeding. Bleeding is usually due to ulceration of gastric or pancreatic tissue in the diverticulum. The acute form is found mainly in patients under 2 years of age. Transfusion of these patients is indicated preoperatively and it is best to raise the blood level to 8-10 gm. of hemoglobin before surgery is attempted. Intussusception is a rare complication but when it occurs the obstruction is usually sudden and complete. After the intussusception is reduced the diverticulum should be excised. Intestinal obstruction is a complication seen in older children. The mortality rate is high because strangulation of the gut takes place rapidly and patients are not usually seen by the surgeon early enough in the course of their disease.

FRANK G. VAL DEZ.

NORINDER, E. AND GAY, R. Preoperatively diagnosed ileus due to gall stone. *Acta Radiol.*, 30: 479 (Dec.) 1948.

Calculi cause ileus in 3 per cent of cases. The passage of the stone itself from gall bladder to duodenum is symptomless, and follows inflammatory adhesion and gradual perforation. Preoperative diagnosis of gall stone ileus is unusual and, including 5 of the authors' cases, totals only 45 cases reported in the literature. Radiopaque calculi are in a minority, 11 of 45 being formed in preoperatively diagnosed cases. A small contrast meal, most useful in proximal obstruction, is the only possible method of accurately diagnosing fistula, as well as ileus and stone. While the presence of air, contrast medium, or both in the biliary tracts is extremely important in the diagnosis of internal fistula, it is not absolute proof of such a diagnosis. Roentgenologically, the diagnosis of gall stone ileus is based on the triad of ileus, fistula, and stone. Enterotomy is the procedure of choice for the removal of the obstructing calculi.

All 5 cases had a previous history of cholelithiasis or upper abdominal complaints, suddenly developing an acute ileus of the small intestine. The flat plates alone in 2 cases revealed ileus with radiopaque calculi, but the contrast meal was necessary in the last 3.

In the latter, barium visualized the gall bladder, common bile duct and in 1 case, the cystic, hepatic and intrahepatic ducts. In none of the cases was gas in the bile ducts evident on X-ray.

A. I. FRIEDMAN.

ROSSMILLER, H. R. AND CRILE, G. JR. Surgical treatment of regional enteritis. *Surg. Clinics N. Am.*, 1133: (Oct.) 1948.

The authors state that the positive preoperative diagnosis of regional enteritis depends on roentgenologic examination but a presumptive diagnosis may be made on history and physical examination alone. The medical treatment for the disease is reviewed and should be reserved for the acute and mild chronic cases and for those with diffuse involvement. Surgery is recommended for those cases, without obstruction or fistula, which fail to enter a remission after medical treatment. In some cases, acute regional enteritis is reversible and should be treated by conservative measures before more radical procedures are undertaken. High doses of penicillin may be of benefit in these cases.

A side-to-side anastomosis without exclusion of the diseased segment rarely results in a long-standing remission of symptoms. However, anastomosis with division of the bowel and exclusion of the involved segment usually does cause a remission of symptoms.

FRANK G. VAL DEZ.

FRIMANN-DAHL, J. Roentgenological examinations of ileus. *Acta Radiol.*, 28: 331 (Aug.) 1947.

The author suggests the following classification of ileus into mechanical and functional types as follows: *mechanical*—(1) obturation ileus, (2) obstruction ileus, (3) strangulation ileus, and (4) volvulus ileus; *functional*—(1) paralytic with peritonitis, (2) non-vascular. The distinction between simple obstructive and true strangulation ileus is often critical. The latter is characterized by severe initial pain, shock, immediate and continuous vomiting, diffuse meteorism, and passage of mucus and blood, but no feces or flatus. A tumor is often palpable but peristalsis is rarely heard. Radiologically, only scanty gas bubbles in the fluid-

filled loops of the small intestine are seen; there is no gas in the colon, and a tumor-like opacity with multicircular outline is usually visible.

In simple mechanical ileus, the onset is insidious. On X-ray, the loops of small intestine are distended, hoop-shaped, with horizontal fluid levels. Fluoroscopy in the erect position reveals that these fluid levels rise and fall as a result of peristaltic motion in the small bowel. The diaphragm is free. The colon usually contains no gas and may not be visible. Solid scybalous masses indicate the absence of infection. Often there is exudation of fluid into the peritoneal cavity. If ileus persists, the circular folds of Kerkringi, sharper in the jejunum and less prominent in the ileum, extend as bands across the abdomen, upwards and to the left in a step-ladder effect. In paralytic ileus, the large and small bowel are distended, the fluid levels in the intestinal loops do not move. There is gas in the stomach. The colonic contents are fluid and there is costo-phrenic fluid and basal atelectasis in the lungs.

In a series of 300 cases, 65 per cent showed X-ray signs of ileus, and 14 per cent were diagnosed as strangulation ileus. Roentgen diagnosis was positive within 6 hours, and the signs became more absolute with time. Therefore repeat studies are recommended. Barium may be used both as contrast enema or by mouth (1-2 tablespoons). In small quantities, there is no danger of obstruction by the barium, and its diagnostic advantages more than offset any possible delay in treatment.

A. I. FRIEDMAN.

JONES, T. E. Surgical management of carcinoma of the colon and rectum. *Surg. Clinics N. Am.*, 1159 (Oct.) 1948.

The need for early diagnosis in carcinoma of the colon and rectum is stressed. With regard to choice of surgical method, the fundamental consideration is that the operation be as extensive and as radical as possible. Lesions in the right colon—whether in the cecum, ascending colon or hepatic flexure—are best treated by right colectomy with side-to-side open anastomosis. Tension on the suture line is prevented by Miller-

Abbott tube decompression started on the day prior to surgery. The modified Mikulicz pack is used to protect the small intestine from areas denuded of peritoneum by the resection; thus the chance of future obstruction is reduced.

In carcinoma of the transverse colon, the author prefers the one-stage procedure with resection performed in the manner best suited to the case. He also believes it is important to do a complimentary tube cecostomy. He has applied the Rankin modification of the Mikulicz procedure in 117 cases. The mortality rate in this group was 5 per cent. In carcinoma of the rectum and rectosigmoid, he recommends one-stage abdominoperineal resection. This offers the lowest morbidity from local recurrences, the lowest mortality, and the greatest palliation.

FRANK G. VAL DEZ

LIVER AND GALL BLADDER

MORTON, R. S. Syringe-transmitted jaundice. An inquiry and a plea. *Brit. Med. J.*, 4586: 938 (Nov.) 1948.

An investigation was made into the continued incidence of jaundice in a clinic for the treatment of venereal diseases, where sterilization was believed to be adequate. Possibilities of transference of hepatitis arose from the re-use of unsterilized syringes, the repeated use of the gallipot without sterilization, the withdrawal of water from the "dirty" bowel into used syringes, and the inadequate boiling of syringes. Other possible sources of infection were syringes employed for injecting penicillin and bismuth and for the collection of blood. Recommendations are made for proper sterilization of equipment and for conditions conducive to easy supervision and for a simple technique for withdrawal of blood and administration of medicaments.

JOSEPH B. KIRSNER.

MALMROS, H., WILANDER, O. AND HERNER, B. Inoculation hepatitis. *Brit. Med. J.*, 4586: 936 (Nov.) 1948.

The authors direct attention to the risk of transferring the virus of hepatitis at: (1) transfusions of blood, plasma and serum; (2) protective inoculations with human

serum as lymph; (3) injections, intravenous as well as intramuscular, unless sterile syringes are used; and (4) blood-sampling, whether of venous or of capillary blood.

An outbreak of hepatitis in 34 individuals, 28 of whom were diabetics, was traced to a so-called "blood-gun" used in the withdrawal of capillary blood from the fingers or ear for the measurement of the blood sugar. Three months after this technique was discarded, the epidemic ceased. By the use of sodium fluorescein solution under ultra-violet light, a model experiment was conducted, demonstrating the risk of transmission of infection if non-sterile syringes are utilized for venipuncture. The danger of infection can be eliminated (a) by the use of sterile needles alone without syringes at venipuncture; and (b) by the provision of a sufficient number of syringes, so that a freshly sterilized instrument is available for every patient.

JOSEPH B. KIRSNER.

MORTON, C. B., II Postcholecystectomy symptoms due to cystic duct remnant. *Surgery*, 24: 779 (Nov.) 1948.

This history of 7 cases is presented, in which postcholecystectomy symptoms were completely relieved through removal of remnants of the cystic duct. In 2 additional cases, such remnants contributed secondarily to postcholecystectomy symptoms. Postcholecystectomy symptoms, occurring 9 months to 18 years after removal of the gall bladder, required surgical relief. Presenting symptoms included pain and jaundice, often of marked degree. The preoperative diagnosis was uniformly the suspicion of stone in the common duct. Surgery included accurate exposure of the extrahepatic ducts, and exploration through probing as well as irrigation. In all cases, complete symptomatic relief was obtained, the follow-up period varying between $1\frac{1}{2}$ and $7\frac{1}{2}$ years. During cholecystectomy, the integrity of the common duct must be protected, but such precaution should never prevent removal of the cystic duct in its entirety. The cystic duct may present extreme variations in length as well as in its course. It may sometimes be so intimately connected with the common duct as to simulate union. Previously, various theories

regarding the causes of postcholecystectomy symptoms had been formulated, especially one ascribing the condition to dilatation of the remnant of the diseased cystic duct and formation of a gall bladder-like diverticulum. Infection and edema may result in extraneous pressure to the adjacent common duct, thus producing widespread cholangitis and hepatitis with their characteristic clinical manifestations of pain and jaundice.

L. T. ROSENTHAL.

McKELL, D. McC., JR. Diagnosis of diseases of the gallbladder. *Surg. Clinics N. Am.*, 569 (June) 1948.

In chronic cholecystitis and cholelithiasis, a history of mild to severe pain in right upper quadrant characteristically radiating to scapula is often obtained. Examination usually reveals some tenderness over the gall bladder area. Duodenal drainage often shows cholesterol crystals and calcium bilirubinate stones. Serum bilirubin may be elevated but it is rarely above 2.0 mgm. per cent. Cholecystography usually demonstrates the stones. Nonvisualization plus a significant history will establish diagnosis of cholecystitis and lithiasis in 95-100 per cent of cases.

In acute cholecystitis, a history of previous attacks is important. The temperature is usually 100-102°. Tenderness, sometimes associated with a mass, is found in the gall bladder. The Graham-Cole test may show faint visualization or stones. Perforation with peritonitis is suggested during an attack of acute cholecystitis by an increase in size or tenderness of the gall bladder, deepening of the toxic state, and a rise in leukocyte count or in temperature. Perforation with internal biliary fistula is suggested by a persistence of tenderness and thickening after the acute cholecystitis subsides. Air may be seen in the liver radicles, and a barium meal may demonstrate the tract. Hydrops appears as a large nontender mass with no visualization on cholecystography. Benign tumors of the gall bladder are infrequently demonstrated with cholecystography; malignant tumors have insidious onset, are more frequent in females, and may have a palpable mass.

FRANK G. VAL DEZ.

PENHAM, B. O. Pathogenesis of hepato-jaundice and its surgical approach. *Am. J. Dig. Dis.*, 16: 397 (Dec.) 1948.

The author discusses 12 cases of jaundice due to liver disease in which operation for common duct drainage was performed. Three of the patients were found to have duodenal ulcer on the anterior wall that did not cause any symptoms. It is suggested that this tendency to ulcer formation is compatible with the presence of disturbed neuro-muscular function of the duodenum with dilatation and stasis. It was observed that, at the time of operation, bile flow, which had ceased sometime before, began with manipulation of the common duct or simple opening of the common duct. It is suggested, therefore, that along with the disturbed excretion of bile incident to liver dysfunction, there is paralysis of the entire bile duct system including the gall bladder. This may be the result of toxic damage to the branches of the splanchnic nerve. Four of the patients died following operation; 8 recovered completely. This recovery is ascribed to the release of bile flow, and the resumption of excretory function of the liver.

HENRY TUMEN.

BJÖRNEBOE, M. Studies on the serum proteins in hepatitis. III—Serum protein variations in chronic hepatitis and the clinical course of the disease. *Acta Med. Scand.*, 132: 170 (Dec.) 1948.

The author reports a study of 18 women and 3 men with severe hepatitis, in whom the variations in icteric index, Takata reaction, serum albumin, and serum globulin are recorded. Twelve of the female patients died of the disease. Among those who died, 10 had a gradual fall in albumin concentration and the remaining 2 had an initial rise followed by a fall in albumin. Values of serum albumin under 3 per cent were usually, but not invariably, accompanied by edema and ascites. The fall in albumin was attributed to a decreased production by liver cells. Low albumin values were usually accompanied by elevations in serum globulin. The Takata reaction closely paralleled the fluctuations in the albumin-globulin ratio. No patient survived if the albumin concentration fell to below 2.48 per cent.

CHARLES A. FLOOD.

DEENSTRA, H. On serum bilirubin during the course of an icterus. *Acta Med. Scand.*, **132**: 223 (Dec.) 1948.

Studies are reported on changes in the rate of the diazo reaction in the determination of bilirubin during various stages of jaundice. The author found that in patients with rapidly changing jaundice, the rate of the diazo reaction tended to increase or decrease as the jaundice increased or decreased. However, as jaundice cleared up, an increase in the rate of the diazo reaction was again noted. The changes observed appear to be attributable in part to the absorption of bilirubin by albumin in the serum. Additional unknown factors evidently also play a role. The increase in the rate of the diazo reaction, noted as the jaundice disappears, is unexplained.

CHARLES A. FLOOD.

SALVESEN, H. A. AND LODOEN, O. Variations in the serum proteins in liver diseases with special reference to their diagnostic significance. *Acta Med. Scand.*, **130**: 525 (June) 1948.

The serum proteins were studied in a large series of patients with hepatobiliary disease. This determination is of value as an aid in the differential diagnosis of jaundice. When the albumin-globulin ratio falls below 0.90, a hepatitis or cirrhosis is probably present. Of 34 determinations in acute benign hepatitis, the A/G ratio was less than 1.0 in 18 instances. In hepatitis ending fatally or becoming chronic, the A/G ratio was usually below 1, whereas in cirrhosis of the liver, it was always below 1.

In common duct stone with icterus, the A/G ratios were always above 1, except when cholangiolitic cirrhosis developed. In obstructive jaundice due to cancer, the ratio was always lowered, but never fell below 0.9 except in far advanced cases.

CHARLES A. FLOOD.

LUPS, S. AND FRANCKE, C. Observations on the occurrence of yellow pigments different from bilirubin and carotinoids in sera of healthy persons and icteric patients. *Acta Med. Scand.*, **129**: 234 (Nov.) 1947.

Yellow pigments, which do not form a diazo compound and are not carotinoids, have been described in normal and icteric

sera. Previous investigators have reported the finding of yellow pigments soluble in alcohol and presenting a maximum extinction at wave lengths less than 4,400 Å. In the present study, the authors were unable to demonstrate the existence of such pigments by photospectrometric methods.

The ratio of yellow pigments, forming a diazo compound, to the total amount of yellow pigments, excluding carotinoids, in sera obtained from patients during and immediately after the disappearance of jaundice, was found to be significantly lower than in the sera of healthy persons. This observation may be explained if it is assumed that yellow non-diazo-forming substances, different from carotinoids and differing from the types previously described, are present in such jaundiced sera. An alternative possibility is that all of the bilirubin present in these sera does not react quantitatively to form a diazo compound.

CHARLES A. FLOOD.

ULCER

VOGEL, F. The symptomatology of peptic ulcer. *Rev. Gastroenterol.*, **15**: 922 (Dec.) 1948.

From a review of the symptoms of 400 ulcer patients, one-half with gastric ulcer and one-half with duodenal ulcer, the following conclusions were drawn: In duodenal ulcer, there is a greater variety of irregular sensations, severer pain with radiation to the back, a greater frequency of heartburn, vomiting, hunger, and nocturnal and constant pain. Hematemesis is more frequent in gastric ulcer, but tarry stools occur with about equal frequency in both groups. If pain is referred laterally, there is a tendency toward the left in gastric ulcer, and toward the right in duodenal ulcer. In spite of these generalities, it appears that the site in a characteristic and uncomplicated case of peptic ulcer cannot be differentiated by symptoms alone.

C. WILMER WIRTS, JR.

HANSON, M. E., GROSSMAN, M. I., AND IVY, A. C. Production of gastroduodenal ulcers in the dog by continuous subcutaneous or intravenous administration of histamine. *Surgery*, **24**: 944 (Dec.) 1948.

Daily intramuscular injections of a his-

tamine-beeswax mixture (30-40 mg. histamine) have been shown, by Code and Varco, to produce duodenal ulcers in dogs and other animals. Continuous subcutaneous injection of histamine base, at a rate above 1 microgram per kilogram per minute, produced ulcers, usually duodenal, within 2 weeks in the majority of dogs so treated. Ulcer perforation occurred in 7 of 12 animals showing ulcer. The ulcers were often multiple. Two dogs had ulcers at the pyloric sphincter, two in the esophagus and one in the pars intermedia. Varying degrees of colitis were noted at autopsy.

Thirteen of 16 dogs receiving histamine intravenously and continuously (7.5-36 mg. base per day), developed ulcers within 16 days. Perforations occurred in 3 dogs. The lesions were usually located in the duodenum; the stomach was involved in 2 dogs. "Increasing the rate of continuous histamine administration above that which produces maximal gastric secretion increases the severity and rapidity of onset of ulceration, indicating that histamine exerts some additional action to decrease the resistance of the intestinal mucosa to the destructive effect of the gastric juice."

LEMUEL C. MCGEE.

COLP, R. Surgical treatment of gastric, duodenal and gastrojejunal ulcer, including the present status of vagotomy. *Bull. N. Y. Acad. Med.*, 24: 755 (Dec.) 1948.

The author reports on vagotomy performed in 126 cases of duodenal, gastric and jejunal ulcer from December 1, 1945 to February, 1948. The supradiaphragmatic approach was employed in the first 35 patients, and in the remaining 93 cases infradiaphragmatic vagotomy was done. As a result of this study, vagotomy as a sole procedure has been abandoned in the treatment of unobstructed duodenal ulcer because, in a series of 21 cases, 7 required further surgery (2 for recurrent duodenal ulcer, and 5 for gastric dilatation and atony). The completeness of the division of the vagi as evidenced by the insulin test bears no relationship to the clinical results. The addition of gastroenterostomy to vagotomy seems to have eliminated the undesirable effects of gastric atony in 26 cases of duodenal ulcer in which it was performed. Only long range follow-

up studies will determine whether the incidence of gastrojejunal ulceration will be lessened by the combination of vagotomy and gastroenterostomy, as compared to gastroenterostomy alone. In cases of duodenal ulcer unsuitable for subtotal gastrectomy, gastroenterostomy combined with bilateral infradiaphragmatic vagotomy is the preferred procedure. Subtotal gastrectomy still remains the operation of choice in duodenal ulcer. It has been combined with infradiaphragmatic vagotomy in a series of patients whose preoperative acidity was high and who had a tendency to bleed. There has been no increase in the operative mortality and a slight increase in the postoperative morbidity attributable to the added vagotomy. Whether the incidence of recurrent gastrojejunal ulceration will be lessened remains a subject for further study. The immediate results of vagotomy in the therapy of gastrojejunal ulceration, following gastroenterostomy and subtotal gastrectomy, have been excellent. However, subsequent follow-up has revealed recurrent ulceration in some cases. In patients considered to be good operative risks, a subtotal gastrectomy with infradiaphragmatic vagotomy for gastrojejunal ulceration following gastroenterostomy is preferable to vagotomy alone. Wherever possible, in gastrojejunal ulceration following subtotal gastrectomy, resection of the ulcer and further gastric resection combined with infradiaphragmatic vagotomy would seem preferable to the severance of the vagus nerves alone. Finally, vagotomy is definitely not indicated in the treatment of gastric ulcer.

ALBERT CORNELL.

LIPS, A. C. M., VERSCHURE, J. C. M., AND STRENGERS, T. The histamine level of the blood in patients with gastric or duodenal ulcer before and after treatment with aluminum hydroxide. *Acta Med. Scand.*, 129: 276 (Nov.) 1947.

The histamine level of the blood was determined in 60 patients with peptic ulcer. Normal values were obtained in 50 patients in this group. There was no correlation between the secretion of gastric acid and the histamine level of the blood. This is in contradiction to the findings of Teorell. Following a period of treatment with diet

and aluminum hydroxide, the histamine content of the blood was usually increased. It is postulated that this observed increase in histamine may be due to a change in intestinal flora or to a reabsorption of inflamed tissue in the region of the ulcer which has been shown to be rich in histamine.

CHARLES A. FLOOD.

FUREY, W. W. X-ray observations before and after vagotomy. *Radiol.*, 51: 806 (Dec.) 1948.

The radiologist should be familiar with the vagotomy controversy and with the pertinent clinical and laboratory findings and thus know what to expect when asked to study one of these patients. The author demonstrates some of the occasionally startling and paradoxical roentgen findings. It is rather striking to have a patient appear well and state that he feels fine, has no distress, eats everything, sleeps well and has gained weight since operation, and then to find, that his stomach is markedly distended, and contains considerable quantities of retained food material. Such stomachs retain opaque material almost completely—in some instances, for a 24 hour period. There is great difficulty in visualizing the duodenal bulb. However when it is demonstrated, there is frequently a marked deformity. Sometimes, there is evidence of a persisting ulcer crater in the complete absence of pain or tenderness on direct palpation.

FRANZ J. LUST.

CRILE, G. JR. The surgical treatment of peptic ulcer. *Surg. Clinics N. Am.*, 1123 (Oct.) 1948.

The treatment of gastric ulcer is primarily surgical. All large gastric ulcers, all recurrent gastric ulcers, and all gastric ulcers persisting in spite of adequate medical management for one month, should be resected. Gastric resection is the treatment of choice. When the ulcer is very high, vagotomy with biopsy of the ulcer may be done. A third procedure well adapted to small ulcers is vagotomy with excision of the ulcer and gastroenterostomy. Vagotomy alone should not be done because of the danger of an existing carcinoma.

Duodenal ulcer is primarily a medical problem and operation should not be advised until medical management has been given a fair trial. The authors state that their results, obtained with vagotomy and gastroenterostomy or pyloroplasty, justify this procedure as the treatment of choice when surgical intervention is indicated for duodenal ulcer. After 2½ years experience, they believe that transabdominal vagotomy with pyloroplasty or gastroenterostomy for duodenal ulcer is safer than gastric resection, more effective than gastric resection in controlling the tendency to recurrent ulceration, and attended with less morbidity and disability than is gastric resection.

With jejunal ulcer, the preferred treatment is transabdominal vagotomy if no obstruction is present. If obstruction is present, a vagotomy should be performed, the old gastroenterostomy taken down and a new one made.

The reasons for preference of transabdominal over transthoracic vagotomy are listed. The surgical anatomy of the vagus is discussed as is the technic of vagotomy, preparation for operation, identification of the vagus and postoperative course.

FRANK G. VAL DEZ.

RUSSELL, W. A., WEINTRAUB, S., AND TEMPLE, H. L. An analysis of X-ray findings in 405 cases of benign gastric and pyloric ulcer. *Radiol.*, 51: 790 (Dec.) 1948.

The confusion in anatomical terminology with reference to the stomach is emphasized, and a plea is made for the adoption of precise nomenclature to be used and understood equally well by the roentgenologist, surgeon, and pathologist.

Of 429 ulcers in 405 cases, 65 per cent occurred on the lesser curvature of the body of the stomach, including the region of the incisura angularis. A relatively high number (8%) were located in the prepyloric area; 19 occurred at the pylorus. The radiographic criteria for diagnosis of pyloric ulcers are given. The reason for the discrepancies between the radiographic and surgical location of a lesion, particularly in the region of the pylorus, are discussed. It is the opinion of the authors that the X-ray diagnosis of

location is by far the most accurate method. A comparison is made between the results of the medical and surgical treatment in patients requiring hospitalization. The treatment of choice is gastric resection, which showed 92 per cent good results as compared with 41 per cent with medical management. Multiple gastric ulcers were observed in 23 cases (5.7%). Triple ulcers were seen once. In the case of triple ulcers, and in 10 instances of double ulcers, the lesions were observed simultaneously. Duodenal ulcers, either active or healed, were associated with gastric ulcers in 10 per cent of cases.

FRANZ J. LUST.

PROCTOLOGY

HILL, J. R. AND SMITH, N. D. Colloid adenocarcinoma involving the perianal region, anus, rectum or sigmoid colon. *Am. J. Surg.*, 76: 642 (Dec.) 1948.

Colloid adenocarcinoma of the distal segment of the gastrointestinal tract is often a peculiar and difficult diagnostic problem. Observations were made on 38 cases of colloid adenocarcinoma in the perianal region, anus, rectum and sigmoid colon. The sex distribution was 25 males and 13 females; 11 were under 40 years of age and the remainder were in the fifth, sixth, seventh and eighth decades. Diagnosis is often delayed because the lesion may simulate a benign or inflammatory stricture, anal fistulas or wounds which usually result from fistulectomy, diverticulitis, abscesses and ulceration. Inaccurate diagnoses lead to hemorrhoidectomy, fistulectomy, dilatation, local tumor excision and roentgen therapy. In less than 1 year following the diagnosis, 45 per cent of the patients were dead; 6 died during the second year, 7 during the third year, 3 during the fourth year, and 1 during the sixth year. Repeated biopsy is necessary in the presence of a suspicious lesion in this area and the proper therapy is early radical surgery.

MICHAEL W. SHUTKIN.

TURELL, R. Colonic adenomas. *Am. J. Surg.*, 76: 783 (Dec.) 1948.

The results are reported on sigmoidoscopic examinations in 2 series of cases, including an

asymptomatic group and a group with rectal bleeding. Evaluation of therapy in the latter group is made. In the first group, 386 asymptomatic patients under 45 years of age were subjected to proctosigmoidoscopic examination. Biopsy specimens in the presence of sessile and even pedunculated lesions were taken from the center, periphery, surrounding and basal structures in order to observe infiltration in the muscularis mucosa. Seven polyps and 9 mucosal excrescences in 14 patients were considered benign. A similar investigation of an equal number of older patients complaining primarily of rectal bleeding, revealed 27 adenomatous polyps. Five of the grossly benign-appearing, pedunculated adenomas showed malignant foci in their bodies on histologic examination.

The propensity of colonic adenomas to undergo malignant degeneration makes extirpation mandatory. Endoscopic fulguration is best employed in the treatment of pedunculated and sessile growths. Techniques involve the use of wire snares, special electrically activated clamps, biopsy forceps followed by desiccation, double-loop resector, and transabdominal colotomy. No recurrence appeared in 22 instances with pedunculated polyp, while a 14 per cent recurrence rate followed treatment in the sessile adenoma.

MICHAEL W. SHUTKIN.

SURGERY

FANSLER, W. A. AND FRYKMAN, H. M.

Surgical treatment of non-specific ulcerative colitis. *Am. J. Surg.*, 76: 713 (Dec.) 1948.

Surgery in idiopathic ulcerative colitis may be indicated in the fulminating type, the chronic irreversible septic form intractable to medical management, and also for the prevention of serious complications. There is no yardstick to indicate when conservative measures should be abandoned and surgery employed. Useful operations are: (1) ileostomy alone; (2) ileostomy with complete colectomy, with or without removal of the rectum; (3) partial or complete colectomy with anastomosis of the ileum to the remaining segment of colon or rectum; and (4) vagotomy. In ileoproctostomy, the an-

astomosis should never be made lower than the upper portion of the rectal ampulla, otherwise stricture and incontinence may result.

Transthoracic vagotomy was performed on 4 patients, and the short period of post-operative observation indicates a promising place for this procedure in idiopathic ulcerative colitis. The most striking results have been in the acute fulminating type of the disease, and it is in this group that the highest operative mortality has been previously encountered with emergency ileostomy.

MICHAEL W. SHUTKIN.

MIMPRISS, T. W. AND BIRT, St. J. M. C. Results of partial gastrectomy for peptic ulcer. *Brit. Med. J.*, 4590: 1095 (Dec.) 1948.

An analysis is made, in a series of 248 patients, of the merits of four types of anastomosis used in partial gastrectomy. The following anastomoses were established: (a) End-to-side, with an antecolic proximal loop attached to the greater curvature; (b) end-to-side, with a long antecolic proximal loop attached to the lesser curvature with a valve and small stoma; (c) end-to-side, with a short postcolic proximal loop attached to the lesser curvature with a small valve and a small stoma; and (d) end-to-side (Billroth I type) joining the duodenum to the greater curvature of the stomach.

The mortality rate for partial gastrectomy in peptic ulcer was 2 per cent. Eighty per cent of operations for duodenal ulcer were classified as good, as compared with 58 per cent for gastric ulcer. In both types of ulcer, the incidence of poor results was 5 per cent. With the exception of anastomosis of the afferent loop to the greater curvature, which leads to a high incidence of proximal-loop filling, the functional results of the other three anastomoses were similar. The long proximal loop needed in the antecolic operation is more likely to lead to complications than the short loop used in the retrocolic operation. The Billroth I anastomosis is probably the safest, since it has no afferent loop. Owing to the risk of stenosis however,

this is not a suitable anastomosis after gastrectomy for duodenal ulcer.

JOSEPH B. KIRSNER.

PATHOLOGY

HELWIG, F. C. Role of the pathologist in the diagnosis of polypoid lesions of the colon and rectum. *Am. J. Surg.*, 76: 728 (Dec.) 1948.

Pathologists, confronted by new diagnostic refinements, are earnestly aroused to re-evaluate neoplastic disease including the border-line epithelial growths of the colon and rectum. Simple hyperplasia is the first step in adenoma formation. This hyperplasia in most instances seems to arise *de novo* from normal-appearing mucosa without the intervention of any demonstrable etiologic agent; no known etiologic factor has been convincingly demonstrated. The pathologist should receive the whole tumor, including the base, and also a complete description of the gross appearance of the tumor. Ulceration and/or induration of the base of the polyp usually indicates clinical carcinoma. Papillomas are broad-based, soft, and frequently cover wide areas. As they enlarge, they tend to reveal the same cellular variants observed in adenomas. Unlike adenomas however, these tumors are more apt to undergo malignant changes at the base, and, because of relative large size, are treacherous. Biopsy from basal ulceration and induration should be made.

MICHAEL W. SHUTKIN.

PHYSIOLOGY: SECRETION

KAHLSON, G. The nervous and humoral control of gastric secretion. *Brit. Med. J.*, 4590: 1091 (Dec.) 1948.

On the basis of experiments carried out chiefly by Uvnäs, the author presents the thesis that gastrin is contained in the pyloric mucosa and, in man and pigs, in the duodenum as well. It is liberated by vagus impulses or when chemical substances such as food come in contact with the mucosal regions concerned. The liberated gastrin is carried by the blood to the fundic mucosa, where it causes the release of histamine in quantities sufficient to stimulate the parie-

tal cells. In this concept, gastrin constitutes a common factor in the nervous, gastric and intestinal phases of acid gastric secretion. The author concludes that "much work remains to be done before this view can be accepted even by those who are suggesting it as a working hypothesis."

JOSEPH B. KIRSNER.

PHARMACOLOGY

BRUMMER, P. AND BUNDUL, A. On the effect of some common gastric drugs on the motility of the stomach. *Acta Med. Scand.*, 130: 559 (June) 1948.

The effects of various drugs on gastric tonus and motility were studied by X-ray. Atropine decreased peristalsis and sodium barbital increased it. Papaverine did not affect gastric motility although it depressed tonus in the duodenum. Hydrochloric acid caused increased duodenal peristalsis. Various antacids, including sodium bicarbonate and magnesium salts increased gastric peristalsis. The authors are of the opinion that the benefit derived from the drugs under observation is due to their effect on gastric and duodenal motility. No explanation is available yet as to why one patient obtains more relief from certain drugs, such as sodium bicarbonate, and others find a different drug more beneficial.

CHARLES A. FLOOD.

MISCELLANEOUS

KORNBLUM, S. A. Radiographic pneumoperitoneum in acute perforations of the gastrointestinal tract. *N. Y. State J. Med.*, 48: 2726 (Dec.) 1948.

Eighty-seven cases of acute perforation of the gastro-intestinal tract, subjected to X-ray examination, are the subject of this report. In order of diminishing frequency, the organs perforated were appendix, stomach, duodenum, large bowel, and jejunum and ileum. In 14 cases of perforated appendices, only 1 showed pneumoperitoneum. Sixteen of 27 perforated stomachs, 19 of 27 perforated duodenum, 7 of 11 perforated colons, and 3 of 8 perforated jejunum and ileum cases, showed air in the peritoneal cavity. According to experimental evidence

from cadaver studies, 5-10 ml. of air in the right subphrenic space will cast an X-ray shadow recognizable as such. The reasons for the low incidence of positive X-ray evidence in this small series are given as, (1) adhesions in the right upper quadrant, (2) perforation below the fluid level, (3) absence of gas in the viscus at the time of perforation, (4) plugging of the perforation by gastrointestinal contents or mucosa, and (5) technical difficulties in the X-ray examination.

PHILIP LEVITSKY.

PALAZZO, W. L. AND SCHULZ, M. D. Spindle-cell tumors of the gastro-intestinal tract. *Radiol.*, 51: 779 (Dec.) 1948.

Spindle-cell tumors of the gastrointestinal tract were found in 0.67 per cent of 12,000 necropsies and in 1.2 per cent of 5,313 surgical records at the Massachusetts General Hospital. Both benign and malignant varieties occurred with increasing frequency as age progressed. Of the total 140 spindle-cell tumors, 9 per cent were located in the esophagus, 65 per cent in the stomach, 17 per cent in the small intestine, and 9 per cent in the colon. Spindle-cell tumors accounted for 2.3 per cent of all tumors surgically removed from the esophagus in the past 16 years, for 5 per cent of those in the stomach, for 7 per cent of those in the small intestine, and for 0.2 per cent of those in the colon. Of those spindle-cell tumors found in the esophagus, 33 per cent were malignant; in the stomach, 36 per cent were malignant. Fifty-four per cent of the patients bearing the tumors remained well and free of disease for an average of 8 years. Recurrence of metastasis, if present, was evident within 4 years. Metastasis to the liver and lymph nodes occurred in 33 per cent of the malignant gastric tumors; in the small bowel, 77 per cent were malignant. None of the patients remained free of disease for longer than 3 years. Of the colonic tumors, 86 per cent were malignant; only 1 patient in this group is alive, with no sign of recurrence after 5 years. There are no safe criteria by which the benignity of such tumors can be recognized with certainty.

FRANZ J. LUST.

The plan behind any diet for the relief of constipation is to supply material which will be absorbed in the small intestine to only a limited extent and will largely pass on into the colon and add bulk. Thus, the diet should include adequate amounts of fruits and vegetables. In addition, the intake of adequate amounts of fluids, at least 2.5 to 3.5 liters daily, is of the greatest importance. Since it is so difficult for many individuals to include adequate amounts of fruits and vegetables to provide bulk, the tendency in recent years has been to add a variety of hydrophilous colloids to the diet. Such bulk substances include agar-agar, kelp, acacia, tragacanth, karaya gum, psyllium seeds and many others.

It was natural then that a search should be undertaken for a substance of this type which could be taken by mouth and which would have little or no effect in the stomach and small intestine. Methylcellulose* seems to answer these criteria.

METHYLCELLULOSE

Methylcellulose under the trade name of "cellothyl" has been found to be of particular help to patients who have the syndrome of irritable bowel, associated with either obstinate constipation or frequent stools, patients who have overactive intestines in the presence of intestinal stomas, and patients who have malfunctioning intestines from one cause or another.¹

Methylcellulose is a white, fluffy, cotton-like material dissolving in water to form a colloidal solution. A 0.5 gm. tablet placed in 1 ounce (30 cc.) of lukewarm water dissolves in five to ten minutes, leaving innumerable tiny translucent gelatinous particles 0.5 mm. or less in diameter. It will dissolve in a somewhat similar manner in tap water at room temperature in one and a half hours but in water of this temperature the substance will not actually disintegrate, but will remain as a fluffy substance and when only $\frac{1}{2}$ cup water is used very little of it will disintegrate in a period of one and a half hours. It has been found to pass through the digestive tract unchanged.² Studies on animals suggest that ingested methylcellulose remains in the liquid state throughout most of its passage through the digestive tract so that there is no bulk in the stomach or upper part of the small intestine and bulk does not begin to form until it gets to the lower part of the ileum and colon.³

A number of patients with the syndrome of irritable bowel associated with diarrhea have taken 4 methylcellulose tablets every four hours by mouth with resultant abdominal comfort and reduction of the number of stools. A large number of patients with the syndrome of irritable bowel associated with constipation have received a similar number of tablets of methylcellulose

* Cellothyl tablets are manufactured by Chilcott Laboratories, Division of the Maltine Company, and contain 0.5 gm. of methylcellulose.

with relief of symptoms. These patients were not afflicted with any ordinary form of constipation, for they had taken large quantities or as some of them said "barrels of laxatives" of one kind or another. The results achieved are all the more striking because the patients whose cases are reported as cases 1 to 5 all felt that there was no hope for the relief of their obstinate constipation.

RESULTS OF TREATMENT

Case 1.—A woman, aged 57 years, from Mississippi came to the clinic in August, 1939. She gave a history of having had dyspepsia, gaseous bloating, belching and obstinate constipation since early childhood. The usual anticonstipation program was instituted with some relief. However, the patient had recurrent difficulty. Finally on September 1, 1948, she resumed the anticonstipation diet and took 4 tablets of methylcellulose before each meal and at bedtime. Complete relief of the indigestion and abdominal discomfort occurred and she continued to pass normal soft, formed stools.

Case 2.—A nun, aged 69 years, complained of obstinate constipation of lifelong duration. The usual anticonstipation program had not been helpful. She had been taking laxatives almost daily for as long as she could remember. Various bulk-producing substances had been given without avail. She was given 4 tablets of methylcellulose before meals and at bedtime and in about a week she began having soft stools and two weeks later she reported that she was having the most satisfactory bowel function that she could ever remember.

Case 3.—The patient, a man, aged 44 years who had severe diabetes, had had trouble with abdominal discomfort, gaseous dyspepsia and constipation for many years. He had used various bulk-producing substances without satisfactory results. Four tablets of methylcellulose by mouth every four hours resulted in normal soft, formed stools at the end of the first week and he continued to have these during the period of observation, which lasted for at least a month.

Case 4.—The patient, a woman aged 62 years, had had a carcinoma removed from the sigmoid in January, 1945. As a result of scarring at the site of the resection narrowing occurred and she had great difficulty with evacuation. After 4 tablets of methylcellulose were added every four hours to the usual diet, the stools were changed from hard pellets to a soft, tapioca-like substance and she passed her stools without discomfort.

Case 5.—A woman, aged 19 years, came to the clinic November 1, 1948, because of lifelong indigestion and obstinate constipation. Her mother stated that she had taken a laxative nearly every day of her life since early childhood. The proctoscopic examination showed a rather large rectum and the roentgenologic examination of the colon suggested the presence of a macrocolon. There was no evidence of real megacolon.

An anticonstipation program was instituted and 6 tablets of methylcellulose were given every four hours. At the end of three days the patient complained of most uncomfortable abdominal distention and examination revealed some abdominal distention. As the patient had no other complaints, the program was continued. At the

end of two weeks she was passing stools daily. The stools were fairly large and of a soft texture. Frequent reports from her since then, up to March 1, 1949, indicate that this happy state of affairs has continued.

In these 5 cases of obstinate constipation of long duration, abdominal distention, and discomfort a striking change for the better followed the administration of methylcellulose.

Case 6.—The patient, a man 50 years of age, had undergone ileosigmoidostomy for constipation at a time when this procedure was used. It had resulted in increased dysfunction rather than relief. The patient had suffered for many years before and after the ileosigmoidostomy. After several weeks on using a suitable diet with the addition of 4 tablets of methylcellulose every four hours, he passed daily a formed, soft stool. Improvement of intestinal function began six days after administration of these tablets was begun and continued for ten days thereafter, during which time he was under our observation. He also reported satisfactory intestinal function during the months immediately after he left the clinic.

Besides the 6 patients whose cases I have reported in detail many others who had diarrhea or similar complaints have been given methylcellulose. Brief mention of them will be made.

Twenty patients who had stomas of the sigmoid and who had loose to watery fecal discharges which caused them considerable discomfort were given 6 tablets of methylcellulose every four hours. Twenty-four hours after this treatment was started, the number of stools decreased and the stools took on a soft jelly-like consistency.

Six patients who had had stomas in the distal portion of the ileum because of chronic ulcerative colitis had numerous liquid discharges from the ileac stoma. Six tablets of methylcellulose, given four times a day, resulted in a definite change from a watery to a jelly-like or gummy discharge. One patient who had been passing fifteen to twenty watery stools daily had a reduction after seventy-two hours of treatment to eight stools in twenty-four hours. The discharges were of a mucoid consistency.

Four patients with high ileac stomas are of especial importance because in these the jelly-like particles could be seen floating in an otherwise liquid stool without any evidence of jellying of the discharge as a whole. This observation tends to confirm the findings in animals; namely, that the solution changes to a jelly as it passes down the digestive tract. In other words, this substance is transformed as water is removed and the concentration of the methylcellulose is increased into a colloidal solution.

In several cases of regional ileitis, the rectal stools changed from loose, watery discharges to soft, jelly-like discharges. However, in cases of advanced ulcerative colitis when much of the large intestine was damaged, the change was

not noteworthy. In fact, in some cases, there was no change whatsoever. The reason for this may have to do with the rapid transport of the food residue through the intestinal tract.

Some individuals who were unhappy because of anal incontinence, or a sphincter paralysis, the result of a spinal injury, were made much more comfortable through the addition of methylcellulose to their intake of food.

COMMENT

Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared, in such conditions as the syndrome of irritable bowel associated with either constipation or diarrhea, intestinal stomas and the milder forms of intestinal infections associated with diarrhea. It is of little value in the severe forms of diarrhea, such as that of extensive ulcerative colitis, possibly because the transport of intestinal content is too rapid to allow the necessary change in the methylcellulose.

It is likely that after the initial control of the intestinal activity, a smaller amount of the methylcellulose will continue the early satisfactory results. Schweig¹ has found that as little as 2 tablets per day will maintain normal function.

The use of methylcellulose does not constitute a so-called cure for the several intestinal dysfunctions discussed. It represents a valuable addition to a well-ordered program of the medical care for the conditions mentioned, which often constitutes the difference between happiness and unhappiness of the individual afflicted with that symptom.

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HIDDEN GASTRODUODENAL LESIONS

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With the ever increasing trend toward specialization, there is a growing tendency on the part of physicians to let the radiologist make the diagnosis of gastroduodenal lesions. There is a tendency to neglect the study of the clinical history and physical findings in favor of the more dramatic roentgen method of gastroduodenal study.

There is a small group of patients with definite gastroduodenal lesions which appear to be beyond the diagnostic horizon of the most skillful radiologist. Fortunately the percentage of cases in this group with so-called "hidden gastroduodenal lesions" is small, but is nevertheless very important. Some physicians blame the radiologist who is supposed to be one hundred percent accurate in his diagnoses. Even the most skillful radiologist will readily admit that this ideal of accuracy is not possible. For this reason, it is important that the surgeon study the clinical history and physical findings and correlate them with the radiological findings. By so doing, the x-ray is used as a laboratory procedure to corroborate or disprove our clinical observations. In this way, many cases with "hidden gastroduodenal lesions" would be picked up clinically even though the radiological findings were negative.

Pathology in the biliary system may produce symptoms highly suggestive of gastroduodenal lesions. A roentgen report of non visualization of the gall bladder is no evidence that a gastroduodenal lesion may not also be present. It is not uncommon to find non visualization of the gallbladder and a negative roentgen report relative to the stomach and duodenum and yet at operation the surgeon may find a normal gallbladder and an active ulcer of the duodenum particularly at the pylorus. The correlation of the observations of our physical senses with a judicious attention to the clinical history will make it possible to diagnose gastroduodenal lesions that have been missed by the radiologist.

The radiologist may report a gastroduodenal lesion when the attending physician had no hint of its existence. This is especially true in the diagnosis of early gastric neoplasms. These patients often present little or nothing in the history or physical examination that would lead to a suspicion that a gastric lesion was present.

It should be quite apparent that it is only by the close cooperation of internist, surgeon and radiologist working as a team, that errors can be avoided.

It is not rare for the surgeon to fail to make a definite diagnosis of a gastroduodenal lesion even with the abdomen open. This is especially true in patients operated upon for the second or third time. In such cases, the gastroduodenal

area may be so covered by adhesions that the lesion may be overlooked. Such errors are often due to a failure to dig beneath the obvious pathology to seek out the deeper lying true "hidden gastroduodenal lesions".

The following five cases have been selected to exemplify this type of case.

CASE REPORTS

Case # 1: E. M., age 38, white, female, was admitted to the hospital on Nov. 30, 1947 complaining of pain in the right upper quadrant. This pain was of eight years duration. It was sharp and would come on intermittently. Jaundice was noted on two occasions with clay colored stools. Cholecystogram revealed a non functioning gallbladder with a stone at the opening of the cystic duct. She was treated for a stomach ulcer nineteen years ago. Roentgenograms on Dec. 1, 1947 showed no evidence of active gastroduodenal disease. There was some evidence of a healed duodenal ulcer.

On Dec. 3, 1947 her abdomen was opened. The gallbladder was found to be normal. Near the cystic duct the gallbladder was firmly adherent to the duodenum which was enormously edematous. A penetrating posterior wall ulcer could be felt. The patient had not been prepared for gastric surgery. The abdomen was therefore closed.

On Dec. 11, 1947 the abdomen was re-opened. The duodenum was found to be still markedly edematous. A bilateral vagotomy with posterior gastroenterostomy was done. The edema of the duodenum was such that partial gastrectomy could not be done safely.

Follow-up: The patient has been perfectly well since operation.

Comment

We were erroneously led to the conclusion that this patient was suffering from biliary disease because of the roentgen observations. Except for a history of ulcer nineteen years previously, there was nothing to suggest an active gastroduodenal lesion.

Case # 2: P. J., a fifty-one year old white woman was admitted to the hospital Sept. 7, 1947 complaining of cramping pain in the epigastrium. The pain came on after meals and radiated to her back. It was associated with nausea and vomiting. No hematemeses. For the past three months she had complained of anorexia and weakness. Roentgenograms on Aug. 28, 1947 showed an infiltrating lesion involving the prepyloric gastric segment with ulceration.

On Sept. 12, 1947, the abdomen was opened. The prepyloric portion of the stomach was found to be pulled downward by a mass of adhesions. The pylorus and duodenum were adherent to the liver. No tumor was found in the stomach. The stomach was not opened at this time. A free omental graft was placed over the raw surface of the duodenum and the abdomen closed.

Following operation, the patient continued to complain of the same pain. A roentgenogram on Nov. 11, 1947 showed no change in the gastric lesion. On Nov. 25, 1947 the abdomen was re-opened. A mass of adhesions and omentum was found around

the duodenum. With difficulty the first portion of the duodenum and four-fifths of the stomach was resected. An anterior Polya type of anastomosis was done.

Pathological report: chronic gastritis with healed chronic gastric ulcer. Chronic peri-gastritis.

Follow-up: She has been well since operation.

Comment

It would have been good judgment to have opened the stomach at the time of the first operation since we had been unable to demonstrate a gross confirmation of the roentgen findings. We were led to the conclusion that the radiological findings were due to distortion by adhesions so that release of all adhesions was thought to be sufficient. There was nothing palpable in the stomach to confirm the roentgen observations of an infiltrative lesion. Had the stomach been opened at that time the gastric lesion would have been noted and the stomach resected. It is often difficult or impossible to detect a posterior wall ulcer by palpation. When in doubt, as in this case, it is better to open the stomach so that a careful direct visual examination can be carried out than to assume that no lesion was present because it was not palpable.

Case #3: G. B., a forty-three year old white woman was admitted to the hospital October 19, 1948 complaining of pain in the epigastrium. She noted the onset of pain in 1939. It began one to two hours after meals and was relieved by milk, food, and soda. In 1941 she had a cholecystectomy and a posterior gastroenterostomy. Following this operation, she remained free of pain until one year ago. She then noted a return of the epigastric pain. Despite constant adequate medical care, the pain persisted. Roentgenograms on April 10, 1948 showed no evidence of gastroduodenal disease. Night secretory tests, gastroscopy, and test meals were all negative. No organic basis for her complaints could be demonstrated. A tentative diagnosis of neurasthenia was made and the patient given sedatives. From August 1948 until admission to Grace Hospital in October, she suffered almost constantly from pain. It was no longer relieved by sedatives in large doses.

On October 25, 1948 her abdomen was opened. Considerable scarring was found in the duodenum. An active duodenal ulcer was demonstrated. The first portion of the duodenum and four-fifths of the stomach was resected. The posterior gastroenterostomy was taken down. At this point a large jejunal marginal ulcer was found at the stoma of the gastroenterostomy. An end-to-end anastomosis of the jejunum and a Polya type of gastrojejunostomy was done. Convalescence was uneventful.

Follow-up: Complete relief of pain. Mild manifestations of "dumping syndrome" but does not complain of this.

Comment

Radiological examination was negative in different medical centers. Gastroscopy and gastric function tests were negative. A diagnosis of neurasthenia was made because an organic lesion could not be demonstrated.

Case #4: M. J., a fifty-two year old white woman was admitted to the hospital on Nov. 21, 1948 complaining of gnawing epigastric pain radiating to her shoulder blades. This began one year ago. Alkali relieved the pain. For the past six months the pain has been so severe that she has been unable to sleep. She has been under competent medical care during this time but has been unable to obtain relief. Roentgenograms on Jan. 15, 1948 revealed no gastroduodenal lesion. On Aug. 10, 1948 the roentgen studies were repeated at another hospital with negative findings. On Nov. 22, 1948 the radiological studies were repeated at Grace Hospital with the conclusion that she had a distorted duodenal bulb with minimal opacities in the cephalic prepyloric area whose etiology could not be definitely identified.

Past history: In 1927, a local excision for a pyloric ulcer had been done.

On Nov. 29, 1948 her abdomen was opened. The distorted area in the prepyloric portion of the stomach was readily noted. This was the site of the previous operation. No lesion was found in the stomach itself. Beyond the curve of the mid-portion of the duodenum on the lesser curvature, a hard button-like ulcer was palpable. This so called, "duodenal ulcer occulta" was readily noted. A bilateral vagus resection just below the diaphragm was done without gastroenterostomy.

Follow-up: Complete relief of pain.

Comment

This type of duodenal ulcer the "duodenal ulcer occulta" is so called because of the difficulty in establishing a diagnosis by radiology. In such cases, exploratory laparotomy offers the best means for accurate diagnosis and treatment. This patient is a good example of the ineffectiveness of local excision of a gastric ulcer. Recurrence is almost the rule in such cases.

Case #5: T. S., a forty-one year old white woman was admitted to the hospital¹ on Oct. 15, 1944 with a history of vomiting for the past four months. She had vomited at intervals for the past nine years. These spells of vomiting would last for one day or for as long as one month. During these she would lose weight rapidly. There were no clay colored or tarry stools at any time. No abdominal pain at any time. During the past four months she had vomited daily and had lost fifteen pounds. She has had four radiological examinations in the past five years at different clinics. All such studies were reported as being negative. On Oct. 17, 1944 roentgenograms of the gallbladder and gastroduodenal area showed no disease. On Oct. 20, 1944, a Levin tube was passed and continuous suction started. This was continued until Oct. 21, 1944 when she was re-x-rayed. At this time a moderately large ulcer crater on the lesser curvature near the gastric angle was easily noted.

On October 30, 1944 her abdomen was opened. A posterior wall ulcer the size of a twenty-five cent piece was found to have penetrated into the pancreas. A Polya type of gastrojejunostomy was done with partial gastrectomy.

Follow-up: Patient has been well since operation.

Comment

In this patient repeated roentgen studies at four different centers demonstrated no gastroduodenal lesion. The last roentgenograms taken at our own

hospital failed to demonstrate the lesion. Five days later, following gastric suction, a well defined gastric ulcer could be demonstrated. At operation a penetrating posterior wall ulcer was found. It is unlikely that this extensive ulcer developed in the five days between examinations. A reasonable explanation is that the suction removed a tenacious mucous plug from the cavity of the ulcer thus permitting the open crater to be demonstrated by the barium.

Summary

We all recognise the fact that the radiologist can and will diagnose the vast majority of gastroduodenal lesions. Because of the remarkable accuracy with which our present day radiologists diagnose gastroduodenal lesions, we are prone to accept their reports as being final without considering that they represent merely an expression of opinion. The radiologist would be the first to admit that one hundred percent accuracy in diagnosis, although sought for, cannot be realized. In many instances the conditions in the stomach are such that lesions obvious at operation cannot be visualized radiologically. It must also be admitted that the opposite is also true; namely that lesions not apparent to the operating surgeon have been diagnosed by the radiologist.

The five cases which are the subject of this paper exemplify the various types of gastroduodenal lesions in which repeated radiological study failed to demonstrate the lesion. A diagnosis of neurasthenia or psychoneurosis in such patients is not uncommon.

CONCLUSIONS

1. Four patients in whom gastric lesions could not be demonstrated pre-operatively and one patient in whom even at operation the true gastroduodenal lesion was not found, are reported.

2. One should not accept a negative roentgen report as being conclusive if it does not agree with the clinical findings.

3. Even at operation if the stomach is not opened posterior wall ulcerations can be missed.

4. This small group of patients tax the diagnostic acumen of the surgeon, internist, and radiologist. In the final analysis, exploratory operation may be the only method of arriving at an accurate diagnosis.

THE PANCREAS: CONTRIBUTIONS OF CLINICAL INTEREST MADE IN 1948

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The year 1948 revealed an increased interest in diseases of the pancreas, as shown by the unusually large number of reports found in the literature. Moreover, many of these papers show a considerable amount of clinical and experimental data. This is not only true of this country, but also of other countries in the world. Advantage was taken this year of the current list of medical literature published by the Army Medical Library; this enabled us to summarize the year's contributions earlier than had been possible during the past several years, a period in which publication of the Quarterly Cumulative Index Medicus has been delayed.

As in previous reviews, papers were selected for review only when they contained definite objective data as shown by sufficiently detailed case reports or other observations reported in sufficient detail to be valid. Disease of the pancreas limited to the islet tissue was, as previously noted, not considered for review. For the first time since the war, a number of papers published in foreign journals could be reviewed; the number available will doubtless increase with the coming years.

CARCINOMA OF THE PANCREAS

A tremendous number of reports on carcinoma of the pancreas has been reported during 1948. In this review an attempt will be made to divide the cases into two groups—those involving the body and tail, and those localized to the head of the pancreas.

Carcinoma of the Body and Tail.—As in previous years, most observations deal with the difficulty, if not the impossibility of making a bedside diagnosis in the absence of jaundice. An unusually large number of patients were observed with proved carcinoma of the body or tail of the pancreas in which psychiatric therapy was considered or given. In one report¹¹¹ 87 cases were reviewed, of which 9 showed psychiatric problems which seemed important and indeed in 3 presented the major difficulty in the differential diagnosis. All of them seemed to be characterized by a depression, agitation and intractable insomnia. Yet it was clear upon careful analysis that the underlying personality and the total life pattern in each of these cases revealed no neuro-pathic traits.

In one case the psychiatric diagnosis seemed so definitely positive that the patient received 6 insulin and 6 electric shock treatments, with some apparent benefit to the

psychic manifestations, but with obviously no influence on the progressively downhill course. In another case report¹²⁴ a 60 year old male, because of completely negative diagnostic tests, was considered to have a psychoneurosis, which seemed to be the only explanation of his abdominal pain. The pain finally became very severe, and it was accompanied with complete anorexia, and the patient finally died in extreme malnutrition, as is usually the case in this condition. Still another patient was described⁸⁸ who at autopsy showed carcinoma of the head of the pancreas with liver metastasis; while rather unusual it is classified with carcinoma of the body since the patient had no jaundice. The patient had severe pain in the dorsal spine, but because of completely negative findings he was considered to have no organic disease and was therefore sent to a psychiatrist. However, because of the persistent pain, a laminectomy was performed, which was, of course, negative. During his postoperative period he developed definite evidence of phlebothrombosis, which was treated with some improvement by paravertebral novocaine block. However, 3 weeks later he had further thrombosis of the opposite femoral vein which progressed despite all therapy. The femoral vein was opened and the clot was sucked out, but the patient died immediately afterwards. At autopsy thromboses of the right common iliac and inferior vena cava, and multiple emboli in the pulmonary artery were found.

The incidence of peripheral thrombosis in carcinoma of the body and the tail of the pancreas is also shown in another case report¹⁰⁸ in which these manifestations were the initial evidence of the disease. In this case each of the 4 extremities was successively involved. This was followed 15 days later by acute apprehension, delirium and death. At autopsy the tumor was in the tail of the pancreas with extensive metastases. Phlebitis was present in the abdominal veins, including the vena cava. There were also thromboses present in the right ventricle and the pulmonary artery. This was also the finding in another case⁶⁴ of a patient who presented himself with a chief complaint relative to thrombosis of the femoral vein. A second case reported by the same author developed multiple thromboses with leg signs after a diagnosis of carcinoma had been made by previous exploratory laparotomy. At autopsy the diagnosis was verified, the tumor being in the tail of the pancreas with associated multiple venous thromboses. In a clinical pathological survey¹⁰¹ carcinoma of the body and tail was shown to have a longer duration, i.e., 10 to 12 months as compared with carcinoma of the head and neck, i.e., 4 to 6 months. Perhaps this explains much of the diagnostic difficulty since these patients live longer in order to plague the diagnostician.

To confirm the well known difficulty in diagnosis, a series of cases have been described illustrating the impossibility of making an early bedside diagnosis. For example, in one case⁵⁷ a 67 year old male entered the hospital 3 weeks after the onset of abdominal pain and distension. A nodule was found at the site of an old hernia scar which was excised, and contained a metastatic adenocarcinoma. At death 3 months later a well differentiated tumor of the tail of the pancreas was found with extensive metastases. In another case¹⁰⁴ the only evidence found after a 3 months history of epigastric distress and pain in a 59 year old male was x-ray evidence of metastatic lesions in the lungs. At autopsy 5 weeks later the metastases were verified

and found to originate from an undifferentiated adenocarcinoma of the tail of the pancreas with invasion of the spleen and many other organs. In still another report²⁰ a 67 year old male showing merely anorexia, weakness and vague abdominal pain apparently died of liver failure, but at postmortem showed a carcinoma of the body and tail of the pancreas with liver, pleural and peritoneal metastases, the liver being largely replaced by tumor.

The only hopeful report¹⁰ in this dark picture is a history of a 63 year old male whose abdomen was explored because of loss of weight, weakness and a right upper quadrant mass. The patient had no evidence of jaundice whatever. The mass was located in the pancreas and a radical resection of the duodenum and head of the pancreas was carried out; the patient recovered and remain well, without any evidence of recurrence, for 11 months, which was the period of follow-up and with a completely satisfactory nutritional status.

Carcinoma of the Head of the Pancreas.—At least 3 conditions must be considered together since all are associated with jaundice—carcinoma of the head of the pancreas, carcinoma of the ampulla of vater, and carcinoma of the duodenum. In one series of 90 cases³¹, all proved by biopsy or autopsy, the important diagnostic features were discussed. Carcinoma of the ampulla was not differentiated from carcinoma of the head of the pancreas because the primary site was not certain in many instances. The average duration of symptoms was 4.7 months, and pain was present in 75 and jaundice in 60 of the 90 cases. Glycosuria was found in 21 of the 81 cases studied. Positive x-ray findings were obtained in only 35 of the 72 examined.

The diagnostic difficulty even in the presence of jaundice is illustrated in a very interesting report⁹⁷ of 4 cases. In one case the patient had a massive resection, but death occurred on the 17th day and autopsy showed that the carcinoma was primary in the stomach with duodenal and pancreatic invasion. In another case the tumor grew so slowly that diagnosis was finally made only after 2 years of symptoms and 3 operations. In the third case the patient at operation was felt to have a tumor at the ampulla, yet there was no evidence of complete obstruction. Common duct drainage was carried out. Cholangiograms 2 weeks later showed a normal passage into the duodenum, and the patient remained well for 1 year. In the last case a cholecystojejunostomy was done for the relief of jaundice as a first stage to resection. One month later a second operation was performed, but the tumor was found to be already inoperable. A similar observation showing the rapidity with which a carcinoma of the pancreas may grow was reported⁶⁷ of a 58 year old male in which a period of 2 months elapsed between the first stage and the second stage, at which time resection was impossible, although it seemed to be feasible at the time of the first operation. To add further difficulty to the diagnosis of carcinoma, a case of intermittent jaundice is described²¹ in a patient whose last attack subsided completely and he was discharged after 3 weeks of observation in the hospital. Two months later the jaundice recurred; at operation a tumor was found at the ampulla of Vater which was well differentiated and resected without complication.

Enthusiasm for radical resection for carcinoma of the head of the pancreas seems unabated despite disappointing follow-up results, a fairly high mortality and a low incidence of operability varying from about 6 per cent to 30 per cent. In one report¹⁸ of 52 resections, the mortality was 18 per cent. In another series²¹ of 22 cases, it was 27 per cent. Of interest was the fact that in this series there were 5 cases of supposed carcinoma of the ampulla, yet 4 turned out to be really cases of carcinoma of the duodenum. Two died after operation with anuria; 3 were well 18, 42 and 51 months after operation. In another series²¹ 49 cases of radical resection were followed by 13 deaths or a mortality of 26 per cent. In a follow-up of 24 patients who survived surgery, 15 are known to have died of recurrence. Of the 9 who are living without evidence of recurrence, 5 had carcinoma of the ampulla. One patient with carcinoma of the duodenum is also still living. Another series of 22 cases⁷⁸ subjected to radical resection, was followed by a mortality of 27 per cent, although the author states that there were no deaths in the last 6 operations. Another surgeon⁴ operated upon 7 patients with carcinoma of the pancreas, ampulla, or duodenum, reporting that of the 4 which survived, the longest is still living and well at 18 months. The least hopeful experience was that of 6 cases⁷³ subjected to radical resection of which 2 died after operation, the rest of recurrences. One surgeon¹⁹ reported 2 patients who survived radical resection, one 5 years and 2 months, and the other 4 years without evidence of recurrence. The next longest survival is a case of carcinoma of the head of the pancreas¹³ well without evidence of recurrence $3\frac{1}{2}$ years after operation.

That surgeons still carry out local resection is shown by one case report of carcinoma of the ampulla of Vater⁹⁰ in a patient aged 63, who presented a history of 8 months of persistent epigastric pain. Jaundice was first noted on admission. At operation a "thumb" sized ampullary tumor was found which was locally resected together with the adjacent common duct and pancreatic duct with an end to end anastomosis. Pathological diagnosis showed adenocarcinoma. Although the immediate postoperative course was uneventful, there is no follow-up comment. Another instance of local excision of cancer of the ampulla is described in a report from France¹¹⁴ in which a patient with jaundice associated with attacks of abdominal pain was operated upon and through the opening in the duodenum a small tumor of the ampulla of Vater was found and excised locally with an uneventful postoperative course. Follow-up was limited to 4 months. On the other hand, there is one French report⁶³ which is probably the first successful resection for carcinoma of the head of the pancreas in this country. The procedure was carried out in 2 stages.

The results¹⁰¹ in palliative procedures in 57 patients with jaundice from carcinoma of the head of the pancreas showed an average survival of 6.3 months as compared with $3\frac{1}{2}$ months in those who were not operated on. This confirms older observations. An added palliative procedure for relief of pancreatic obstruction was described¹⁸ in which an anastomosis between the pancreatic duct and jejunum was done in 22 cases without mortality.

Unusual experiences were reported which have some interest. In one⁵⁵ a 54 year old patient who developed pain followed by progressive jaundice was found at operation to have a mass at the head of the pancreas which was resected and proved to be

an adenocarcinoma. Recovery was uneventful, but 7 months later he developed a mass in his left thyroid which at operation proved to be a papillary adenocarcinoma, which was removed. A third operation consisted of closure of the biliary fistula which followed the pancreatic resection. This was successful and the patient has remained well for 2 years. At the time of the operation for the closure of the fistula, which was 2 years after the original operation, there was no evidence of recurrence. Four unusual cases²⁶ were described, in one of which a large tumor was resected, including the duodenum, and found to contain necrotic material, i.e., to be a pancreatic abscess which, however, showed no carcinoma. The possibility of doing even more radical resections than have been carried out up until the present is shown by the same author in one patient in which the tumor involved the superior mesenteric vein which was resected and an anastomosis made over a Blakemore tube. Death resulted 8 days after operation from thrombosis in the tube. Carcinoma of the ampulla was compared¹⁰⁰ with carcinoma of the extrahepatic bile ducts. Only one of 10 in the latter group proved to be resectable, yet this patient lived for one year and 4 months. Of the 8 cases of carcinoma of the ampulla, half of them proved resectable. Of the 4 who had radical resection, 2 died, 1 and 6 months after operation, one died 7 years later of melanocarcinoma, and one is living 2 years and 10 months after operation. The need for persistence in attacking carcinoma was shown in a report²⁷ of a 26 year old male who after a radical resection for carcinoma of the ampulla was operated upon a second time because microscopic evidence of carcinoma was found at the resected end of the specimen. At the second operation 3 weeks later the remaining pancreas was removed.

A 55 year old male was described³⁰ in which nocturnal nausea, vomiting and backache was followed by a 25 pound weight loss. Because of the absence of any objective findings the symptoms were considered to be psychoneurotic. However, the patient developed jaundice 2 days after admission and was operated upon with a diagnosis of pancreatitis. However, the nodules which were found at operation and thought to be fat necrosis actually proved to be metastatic carcinoma from a neoplasm in the pancreas. That subsidence of jaundice does not necessarily exclude a diagnosis of carcinoma was shown in a case report¹⁰⁶ of a 69 year old female, who gave a history of jaundice which gradually subsided in the 4 weeks preceding admission. On admission there was definite evidence of cervical metastasis and she died suddenly in shock 30 hours later. At autopsy an adenocarcinoma of the pancreas with extensive spread was found. A similar experience is reported⁹⁴ of a patient who entered with acute sudden severe abdominal pain with an elevated blood amylase. He was operated upon 24 hours later and died several hours following operation. Although operation and autopsy revealed a definitely acute pancreatitis with sanguino-purulent peritonitis, and definite evidence of regurgitation of bile into the pancreatic duct, there was a small carcinoma in the lower third of the common duct extending into the ampulla.

ACUTE PANCREATITIS

Increasing interest in this disease seems indicated by the particularly large number of reports regarding this condition. However, the serum amylase

test is still not extensively used and diagnosis continues to be made for the first time at operation or at autopsy. Moreover, the problem of whether this disease is to be treated entirely conservatively or not, still remains unanswered. While the most frequent type of acute pancreatitis subsides without operation, analysis of many cases seems to indicate that acute pancreatic necrosis, by contrast, is still a great threat to life whether they are operated upon or not.

The largest series of cases of acute pancreatitis⁷⁹ was that of 307 cases in which the diagnosis was made in 159 by means of an elevation in the blood or urinary amylase, 103 by surgery and 45 by the findings at autopsy. Although a complete analysis of this study is not possible, many of the findings are of special interest. For example, several of the patients showed a fall in the blood calcium and occasional electrocardiographic changes. Also of interest is the fact that flat x-ray films of the abdomen showed that 82 out of 125 cases showed the signs usually associated with intestinal obstruction, i.e., segmental ileus most often of the transverse colon. The mortality in this series can be analyzed on the basis of non-operative versus operative treatment, even though there seemed to have been no definite plan as to which therapy should be carried out, and no specific indications for surgery. Of the 204 cases which were treated conservatively and apparently by modern methods, 56 or 27 per cent died. However, of these 16 were admitted in extremis, and undoubtedly were hopeless regardless of therapy. Of the 103 cases operated on there were 46 deaths or a mortality of 44.7 per cent. Of the 46 deaths, exploration only was carried out in 24. On the other hand, 29 cases were subjected to exploration alone and recovered. Unfortunately, no statement is made as to the operative findings in these patients which might be of value in differentiating between acute pancreatic edema and pancreatic necrosis. Of 21 patients who had cholecystostomy alone, 9 died. There were 10 who had a drainage of the pancreas, of which 5 died. Eight cholecystectomies were followed by 5 deaths, whereas 5 patients in whom cholecystostomy was combined with pancreatic drainage, there was a mortality in only one.

It is clear that therapeutic inferences from this tremendous clinical experience is possible, but requires more careful study. If for example it were possible to make a clinical diagnosis in all cases by means of the amylase test on admission, followed by either conservative therapy or by operation at an appropriate interval, results might be obtained which would perhaps give some information as to the indications for surgery and particularly as to the appropriate time for surgery. As it is, the indications for operation were not clearly defined; many patients were operated upon without knowing the diagnosis, thus confusing the picture inasmuch as operation might not have been carried out in many cases had the diagnosis been known. On the other hand, if the diagnosis is known, operation may be planned at some appropriate interval in these cases which do not subside; under these conditions the results would offer convincing proof as to the value or lack of value of operation.

Another complete clinical report⁵¹ deals with an excellent analysis of 80 patients. Of the 22 cases which were designated as hemorrhagic pancreatitis, 5 were admitted in extremis and all died, the diagnosis being made at autopsy. In the remaining 17 cases, operation was carried out. Those in which only a laparotomy was done, all died. Of the 13 in which a cholecystostomy and pancreatic drainage was done, 5 cases survived. Of the 59 cases classified as non-hemorrhagic, 53 were operated upon, the diagnosis being based on the findings at operation. Only 6 were not operated upon, the diagnosis being made on an elevation of blood amylase. Of the cases operated on, 26 were explored under general anesthesia, of which 5 died; 24 under spinal anesthesia, of which 1 died, and 3 under local anesthesia, of which none died, thus indicating that death in non-hemorrhagic pancreatitis may be due more to the anesthetic than to the procedure itself. This seems logical inasmuch as there is no indication for any particular surgical procedure in these cases. Of special interest in this report is the excellent follow-up study. Of the 57 cases that survived, 47 were observed for from 1 to 24 years. Five had recurrences of pancreatitis at intervals of 3 months to 15 years later, and of them, 2 died. Although they previously had only simple edema, the later final attack was of the hemorrhagic form, thus showing that, at least in a few cases, attacks of edematous pancreatitis which subside may be followed by attacks which are definitely hemorrhagic in type. Of 6 patients who had cholecystostomy, stone recurred later.

In another report¹²³ of 33 cases diagnosed by operation, autopsy or elevation of the blood amylase, there were 15 deaths. Twenty-three of the cases were not operated upon, 9 of which died. Of the 10 cases operated upon, 4 died. No differentiation was made on a clinical or pathological basis between the hemorrhagic and non-hemorrhagic disease. A similar lack of differentiation was characteristic of a report⁶⁰ of 30 cases of which 23 were operated upon with a fatal outcome in 6, whereas 7 were not operated upon with mortality in 4 cases. It is obviously difficult and impossible to draw any therapeutic inferences from such experiences. A recommendation for non-operative therapy is voiced following a report¹¹ of 15 cases, all but one of which were operated upon. Based upon the findings at operation, 9 cases had acute pancreatic necrosis, 7 of which died. Three had suppurative pancreatitis, of which 2 died. Three showed acute pancreatic edema; all recovered. This experience is characteristic of previous reports in which the diagnosis is made at the time of operation and thus does not represent a planned program of therapy based upon a bedside diagnosis. Eighteen patients with acute edematous pancreatitis were described,²³ the diagnosis being based upon the finding at operation in 14 with no mortality. Twelve patients were found to have hemorrhagic necrosis, of which 9 died, 4 with and 5 without operation.

A number of single case reports of acute pancreatitis has occurred, only a few of which seem to be of interest. For example, one case⁴² showed a fall in the blood calcium and potassium, evidence of uremia, diabetes, ascites, and bilateral hydrothorax. Death occurred on the 17th day in spite of conservative therapy, including parenteral fluids, calcium gluconate and potassium chloride and blood transfusions. At autopsy there was a general peritonitis with fat necrosis which extended to the pleura and mediastinum. Death also occurred in another patient⁹³ who was treated conservatively for 7 days. He was a 46 year old male who was suddenly seized with upper

abdominal pain and had an elevated amylase. Ten cc. of dark brown peritoneal fluid were aspirated from the abdomen and proved to contain a high amylase content. Treatment was conservative including paravertebral block. At autopsy there was an acute hemorrhagic pancreatitis with marked necrosis of the pancreas and a fatty liver. Conservative therapy was also used in two proved cases of acute pancreatitis.¹¹⁹ In one of them, a 73 year old male, diagnosis was made by high serum amylase. He developed a Gray-Turner and Cullens sign on the sixth day. Treatment consisted of gastrointestinal suction, insulin, parenteral feeding; after a stormy 4 week period, the patient seemed to get well. The second patient developed acute pancreatic necrosis following operation for repair of a hiatus hernia with cholecystectomy, and though treated conservatively with chemotherapy, blood, etc., died, the diagnosis being made at postmortem.

A case of allergic pancreatitis was described,⁹⁸ the diagnosis being based upon the simultaneous presence of generalized urticaria and abdominal pain, associated with an elevation of the blood amylase which gradually returned to normal and the successful response to the administration of pyribenzamine. A case was described³⁷ of a large pancreatic abscess in an 18 months old male child, apparently due to an ascaris which was found in the cavity of the abscess. The patient was operated upon but died 5 days later. The use of the x-ray following barium meal in the diagnosis of acute pancreatitis has been mentioned in previous reviews. Enlargement of the duodenal curve, a distended second portion of the duodenum and elevation of the stomach during acute symptoms have been described⁸³ apparently due to pancreatitis. After the acute symptoms subsided in 3 days, roentgenological signs had disappeared.

An important investigation was made in regard to the influence of acute pancreatitis on cholecystography.¹⁰² In 28 cases of proved acute pancreatitis as judged by elevation of the blood amylase, cholecystogram was performed during the acute phase; in 16 the gallbladder was not visualized. Six of these patients had a subsequent cholecystogram retaken at intervals of 6, 9, 13, 19 and 32 days after the acute symptoms had subsided, whereupon a normal cholecystogram was found. Five of the patients with non-visualization were operated upon after the acute attack of pancreatitis was over. Although the gallbladder was normal in appearance in all, it was excised in 3 and proved to be normal histologically. This study showed first of all that non-visualization of the gallbladder does not necessarily mean persistent disease, and that subsequent study may show normal function. It also showed how acute pancreatitis may be closely related to disease of the gallbladder presumably because a transient obstruction may be produced at the lower end of the common duct by edema of the head of the pancreas.

Pathogenesis of Acute Pancreatitis.—An interesting postmortem study⁷⁵ of the condition of the pancreatic ducts was carried out in an attempt to correlate dilatation of the duct with the presence or absence of pancreatitis. In 100 cases in which there was no evidence of pancreatitis, the ducts and acini were normal in 82 per cent, slightly dilated in 14 per cent, and markedly dilated in only 4 per cent; in 35 cases of pancreatic fat necrosis, there was no

duct or acinar dilatation in 14, and only moderate dilatation in 4, with marked dilatation in only 2; of those with extensive fat necrosis, there was no dilatation in 9, moderate dilatation in 5 and marked dilatation in one. Thus the incidence of dilatation of the pancreatic duct was no greater in patients with fat necrosis than in the control group, suggesting that pancreatitis is not explained by a lesion leading to duct obstruction. Three experimental studies have been made in an attempt to explain the pathogenesis of acute pancreatitis. In one⁶¹ a series of experiments on 64 cats was carried out to show the influence of ligation of the pancreatic duct, of starvation, of feeding, and of secretin and pilocarpine injections. It was clear that ligation of ducts alone in the starved animal was not followed by necrosis. However, obstruction in the fed animal or in the animal whose pancreas has been stimulated by either secretin or pilocarpine led to varying degrees of fat necrosis. Indeed, 14 out of 17 cats, whose pancreatic ducts were ligated and who were fed, showed evidence of fat necrosis between 48 hours and 6 days, even though no pancreatic stimulus by drug was given. In the second study¹⁰⁷ carried out on dogs and rats by a variety of injections into the pancreatic duct either with or without ligation, it was shown in general that activated pancreatic juice, particularly when the duct is ligated produces pancreatic necrosis, an observation which has been made many times in the past. One of the most provocative studies⁸⁶ was the third, which seemed to show one manner in which pancreatic edema may be converted into pancreatic necrosis. Pancreatic edema was produced in all experiments by means of duct ligation followed by the stimulation of the pancreas with secretin injections. However, in addition to this, in 10 dogs, using 7 as controls, varying degrees of occlusion to the main pancreatic artery were produced in a period of 15 minutes. In each experiment, pancreatic necrosis followed the vascular occlusion, and the degree of necrosis varied with the degree of edema present before the arteries were occluded. Inasmuch as vasospasm is known to follow as a reflex action from pain, these experiments seem to have a real clinical application by suggesting the need for prompt control of pancreatic pain.

RECURRENT PANCREATITIS

An increasing number of reports have appeared in regard to the problem of patients who have recurrent attacks of pain. In previous years it was impossible to be sure what these attacks really were, but with the use of the serum amylase test, it is now possible to make a definite diagnosis. As a result, an increasing number of studies have appeared of patients presenting a history of recurring attacks definitely diagnosed as acute pancreatitis. The therapeutic problem here is obviously one of preventing further recurrence of the pain. The problem in those with definite evidence of stone or calcification of the pancreas is a little different and will be discussed under that heading. It should

also be mentioned that the term recurrent pancreatitis is more descriptive than chronic pancreatitis, a designation which has been used widely in the past, but usually as applied to findings at the time of operation. Chronic pancreatitis as a bedside diagnosis has usually been applied to patients who show some disturbance of pancreatic function, although much confusion in the literature has often arisen from the application of anatomical designation to clinical manifestations without anatomical verification.

A series of recurrent pancreatitis has been reported in 2 papers, the first³⁴ describing 5 cases, and the other³⁵ describing in greater detail 21 cases. Many of these patients had a normal gallbladder as shown by cholecystogram or operation, and many of them had had their gallbladders removed previously. All of them had had repeated attacks of abdominal pain, the nature of which was detected by finding an elevation of serum amylase. In many of them a T-tube had been inserted at the time of operation and many physiological studies carried out as to the effect of stimulation of the sphincter of Oddi by installation of hydrochloric acid and other means. Anatomical communication between the common duct and the pancreatic duct as visualized by cholangiogram were demonstrated in many cases. These authors recommend and have carried out in many of these cases a severance of the sphincter of Oddi by a cutting instrument introduced through the common duct. This procedure is supposed to prevent regurgitation of bile and pancreatic juice through a common channel, which is assumed to be the cause of the pancreatitis. Analysis of the findings show that relief was obtained in many of these cases by this procedure. While many of the clinical results were excellent, the follow-up is still too short to evaluate the final results since the longest period of relief of pain was one year. Doubtless further studies will be reported from this clinic later.

Brief mention may be made of a report¹¹⁵ of 11 cases in which operation was carried out for apparently recurrent pancreatitis. The operations were based upon the need for an internal biliary drainage such as an anastomosis between the common duct and the duodenum; although the end results were not discussed in detail, they were described as most gratifying, provided the procedure was carried out before the disease had advanced so that definite chronic pancreatitis was present.

A most complete and interesting study was made of 27 cases⁴³ in which the term chronic relapsing pancreatitis was applied. All of these cases were associated with definite biliary disease. All patients had painful attacks, either associated with or without evidence of diabetes. In many of these seizures there was a definite elevation of the serum amylase. There seems to be no differentiation between this group and 29 similar cases without evidence of gallbladder disease reported previously from this clinic. Twenty-six of the 27 patients were operated upon and a variety of procedures carried out, including cholecystectomy and choledochostomy. In about half the cases there was a remission of the attacks following surgery for up to 11 years. However, in

17 of the 26 cases a secondary operation was carried out. Drainage of the common duct for a period of 2 to 6 months in 8 cases was followed by a cessation of seizures in 5 for a period of between 24 and 36 months after operation. Anastomosis between the common duct and duodenum was carried out in 7 cases, 6 of which had freedom from pain when last seen for periods up to 56 months. Five of the 27 cases have died, one of massive gastrointestinal hemorrhage 2 weeks after operation for cholecystogastrostomy, one of peritonitis and pyelonephritis, one of cardiac failure, one of massive gastrointestinal hemorrhage and one from an unknown cause. In 7 cases biopsy of the pancreas was made and showed various degrees of pancreatitis with fibrosis.

Another thorough clinical study was made in 20 cases designated as chronic recurrent pancreatitis⁶² the diagnosis being based on operative findings in 16, x-ray evidence of calcification of the pancreas in 3, and in one by the findings at autopsy. In 17 of these 20 patients there were definite recurrent attacks of upper abdominal pain with radiation to the back in 6. Eight cases had recurrent jaundice, 5 of whom had definite obstruction of the common duct at operation, none, however, due to stone. Serum amylase was found to be elevated in 3 cases, 2 of them during an attack of pain on admission. Four patients had a normal serum amylase, but 3 of these had no pain at the time. Eight of 9 patients in which glucose tolerance tests were carried out showed a diabetic type curve. Pancreatic calculi were demonstrated in 8 out of the 20 cases. The average age of the patients was 60 years, and 10 of them had had previous operations without relief. Of the 16 who were explored, 3 died, 7 were definitely relieved, 3 were improved, and 3 showed no change. The procedures which seemed to afford some relief were cholecystostomy, cholecystectomy and gastroenterostomy and choledochostomy. Seven cases described as chronic relapsing pancreatitis were described⁵⁰ based upon anatomical findings including biopsy at operation or autopsy. All had recurrent attacks of epigastric right upper quadrant pain. Three cases were completely relieved of pain following anastomosis between the gallbladder and duodenum or stomach. A single case was described⁵ in a 38 year old female who developed increasingly severe attacks of epigastric pain. She also had large, bulky fatty stools and 4 days before admission developed jaundice. At operation during an acute attack fat necrosis with acute pancreatic edema was observed. The gallbladder was drained after removal of its contained stones, but the common duct was not explored. There was an elevation of the blood amylase after operation. The icterus subsided and cholangiograms through the tube in the gallbladder showed multiple stones in the common duct. Clamping the tube produced pain. Irrigation of the biliary tract with nupercaine solution on 2 occasions seemed to relieve pain and apparently was followed by passage of some of the stones since a cholangiogram later showed that only one stone was left. Irrigation was then carried out at 10 day intervals. After 30 days, cholangiograms showed no stones. The catheter was then removed and the patient remained well for a period of 10 months without recurrence of symptoms.

In a series of 7 cases⁵⁶ a diagnosis of chronic relapsing pancreatitis was made from the findings at operation, although the diagnosis was suspected from the clinical

symptoms which consisted of repeated episodes of abdominal pain and back pain with indigestion, nausea and vomiting. Only 2 cases had jaundice and 2 showed evidence of steatorrhea. Calcification of the pancreas was found in 6 cases and cysts in 6. The kind of treatment and follow-up were not mentioned in detail except that bilateral sympthectomy from thoracic 5 through lumbar 2 was carried out in one illustrative case, and in 2 others with complete relief of pain up to a period of 5 months. In another report²³ 5 cases are briefly described in which bilateral sympathectomy was also performed for chronic pancreatitis with gratifying results which, however, were not described in any great detail. Among another series of 6 cases of diffuse pancreatic calcification⁸⁹ diagnosed by x-ray alone in 3 and operation in 3, considerable relief also followed in one case in which a celiac ganglionectomy was carried out, although there was no follow-up.

Pancreatic Calcification.—As is apparent from scrutiny of the cases described above, there is some overlapping of recurrent pancreatitis and calcification of the pancreas, although in most cases the patient with stone in the pancreatic duct has a more constant type of pain which does not seem to occur in definite attacks. Many of them, of course, have other symptoms not associated with pain, and a few are found incidentally, usually by x-ray examination. Thirty-nine cases of pancreatic calcification as revealed by x-ray are described⁴⁴ of which 22 proved to have definite pancreatitis at operation or autopsy. The lapse of time between the onset of pain and the development of pancreatic calcification was from 1 to 22 years. Diabetes was present in 9 and steatorrhea in 7 of the 22 cases of proved pancreatitis. Other associated complications were gastrointestinal hemorrhage in 3 cases, alcoholism in 3 cases, pseudo-cyst in 2 cases, abscess in 1 and neuritis in 1 case. Twenty-one patients were treated by non-operative means and 18 by surgery. The main indication for surgery was severe pain, the objective being first to relieve pain by some means, either removal of a duodenal or common duct obstruction, or of calculi, or to drain abscesses or cysts. Analysis of the results in patients operated upon was very difficult. Procedures carried out were cholecystogastrostomy, -jejunostomy or -duodenostomy, or external drainage by a T-tube. There were no immediate surgical deaths. A 21 year old male with a history of epigastric pain diagnosed originally as periduodenitis finally showed on x-ray evidence of stone in the pancreas.⁴⁰ Because of the severity of the attacks of pain with radiation to the left shoulder, he was operated upon and 8 soft stones were removed from the pancreatic duct and a small cyst excised from the tail of the pancreas. Recovery was uneventful and there was complete relief from pain, although the period of follow-up was not stated. .

Among 35,000 consecutive autopsies, 22 cases of pancreatic lithiasis were found and analyzed.¹⁵ Death was attributable to the pancreatic lesion in only 7 cases, contributory to death in 6 cases and not a factor at all in the remaining

9 cases. There was a definite alcoholic history in 10 of the patients. Sixteen of the 22 cases had multiple stones or diffuse calcification. Only 6 had a solitary stone and 7 had one or more pancreatic cysts. Three had acute pancreatic necrosis, and 2 had evidence of healing fat necrosis, 4 showed purulent inflammation with solitary abscesses. Of interest was an associated fatty liver in 14 and portal cirrhosis in 8 cases. A series of 9 cases is reported³⁸ in which operation was performed presumably for epigastric pain and in which stones were found in the pancreas. Only one patient died. The surviving cases were all markedly improved except one, although some had residual symptoms. The procedure at operation consisted of local removal of stones in 4 cases, nothing but exploration in one case, and in 3 cases removal of stone with partial pancreatectomy. One patient had drainage of the gallbladder with removal of gallstones plus one pancreatic stone. Three cases are reported²⁹ in which the diagnosis was made by x-ray. Two of the patients had evidence of enlargement of the liver.

An unusual case, thoroughly followed for 6 years, is reported⁹² in which the patient between the ages of 39 and 45 years of age had recurrent calculous pancreatitis, as shown by elevation of the serum amylase, by biopsy at operation, and by x-ray evidence of calcification. He was not relieved by cholecystectomy and drainage of the common duct, but developed a gastric ulcer which recurred after medical therapy. A subtotal gastrectomy was then carried out which was followed by a stormy post-operative course. However, the pain was relieved following recovery from operation, steatorrhea was corrected, and the patient gained in weight. Ten months after operation he was entirely relieved, was living a normal life and feeling fine for the first time in 15 years, his diet being restricted only in the amount of fat and alcohol. A 39 year old patient is described³⁹ in whom repeated attacks of upper abdominal pain, anorexia and diarrhea associated with weight loss occurred. A mass was felt in the left upper quadrant and there was a definite elevation of the serum amylase. X-ray showed calcification in the region of the pancreas. At operation the enlarged nodules in the pancreas were biopsied and showed acute and chronic pancreatitis with fibrosis; the gallbladder was normal. Nothing else was done and the patient improved somewhat, but the pain recurred, even though it was less. Radiotherapy was tried without effect. A medically treated case of pancreatitis and diabetes with calcification is described⁶ with somewhat unusual symptoms of pain, chills and fever. The diagnosis was not made until later when x-ray showed calcification and examination of the stools showed steatorrhea. Treatment with insulin and diet alone was followed after 8 months by an increase in weight and a diminution in steatorrhea. Failure of medical treatment was the experience in a case⁹¹ with diabetes, steatorrhea and right upper quadrant pain; pyelonephritis developed which did not respond to chemotherapy and the patient died with an elevated non-protein nitrogen of the blood. At autopsy there was advanced chronic interstitial fibrosis of the pancreas with calculi and cirrhosis of the liver, with a terminal necrotizing renal papillitis.

CYSTIC FIBROSIS OF THE PANCREAS

So many single case reports of this disease have appeared in the literature which add very little to our knowledge, that no attempt will be made to summarize all of them.

Study⁹⁹ of the nitrogen and fat metabolism in 27 cases ranging in age from 6 months to 5 years showed that over a period of 3 days, 5 patients lost 55 per cent of the administered fat. Administration of hydrolyzed protein with or without pancreatin resulted in a much higher degree of nitrogen retention.

A review of 14 cases was reported from Australia⁶⁵ of which 9 have died, all with pulmonary infection as the terminal cause. Twelve of the 14 were females, and 3 gave a definite familial history. Twelve of the cases were over 6 months of age and 2 died at 9 and 10 years of age with severe portal cirrhosis. The presenting symptoms in all cases were those of malnutrition, bowel abnormalities with stools containing a high content of fat, and symptoms of respiratory infection. Tryptic activity of aspirated duodenal contents was uniformly low. Of the fatal cases, 3 had definite inadequate caloric intake, and 8 of the 9 received none or inadequate amounts of pancreatin. Of the 5 patients still living, treatment consisted of the administration of pancreatin, an adequate diet with 30 per cent calculated extra calories, 25 per cent being protein, with added vitamins C and A. These surviving cases are 8 months to 3 years of age, 4 of them being considered to be in a satisfactory condition. The beneficial effect of hyperalimentation was also reported in another more detailed study⁶⁵ to be mentioned later. An islet cell abnormality was found in 5 cases of fibrocystic disease in patients who died at 2 months to 2 years with a typical clinical picture.¹⁰⁹ Histologic study seemed to show one or more duct-like lumens lined with epithelium which seemed to enter small excretory ducts although there was no abnormality of the A and B cells. The significance of this finding in the disease was not apparent.

The association of pancreatic insufficiency with meconium ileus has been suggested before in previous reviews. A report of 8 cases of meconium ileus⁴⁹ is of interest because of the finding of a deficient tryptic activity after duodenal aspiration in many of the cases, and in the fact that all patients were operated upon very early in life, the age at admission being between 10 and 51 hours, and the clinical picture showing definite evidence of small bowel obstruction, confirmed by x-ray study. There was a familial history in 3 cases. In all patients at operation the ileum was opened, and the meconium completely removed by irrigation with a catheter, and in many cases pancreatin introduced into the lumen. Volvulus of a distended loop of the ileum was found in 5 of the 8 cases and in 4 this was simply reduced. There was an immediate operative mortality in 3 of the 8 cases. Four of the patients survived and were in excellent condition 3½ to 26 months afterwards. Postoperative therapy consisted of the use of pancreatin with each feeding, a low fat, high protein diet including hydrolyzed protein, as well as high protein milk and a high vitamin intake, plus chemotherapy. There was no evidence at operation of any gross abnormal anatomical changes in the pancreas. In another report⁴¹ a patient was operated on the third day

of life because of evidence of meconium ileus. Multiple aspirations of the small intestine with a fine needle were done, air being thus removed; the rectum was also opened and much thick, inspissated meconium sucked out. The patient recovered, and stools appeared on the 10th day of life. The acute distension disappeared. At 6 months of age the patient was doing fairly well with a diet containing pancreatin, but showed definite evidence of pulmonary changes characteristic of cystic fibrosis of the pancreas.

Vitamin A absorption curves after oral administration were studied⁶⁴ in 14 normal children, in 14 children with cystic fibrosis of the pancreas established by study of their duodenal content, and in 6 children with steatorrhea of the celiac type. The administration of either emulsified or unemulsified vitamin A produced plasma elevation in the normals. When given to children with steatorrhea the emulsified preparations resulted in normal vitamin A absorption, whereas the unemulsified oil was very poorly absorbed even when given with pancreatin, thus indicating the superiority of vitamin A absorption when administered in the emulsified form. An interesting case report¹⁰³ of cystic fibrosis of the pancreas was described with typical findings except that the duodenal juice showed normal enzymatic activity and the fecal fat was not elevated above normal, although it was foul smelling, large and soft. However, the patient died at 5 months of age and showed ulcerated, suppurative bronchitis, but no bronchiectasis or cystic disease of the lungs. The pancreas showed definite cystic fibrosis which, however, was primarily located in the distal one-half of the gland. The rest of the pancreas showed little if any changes. A fatal case of cystic disease of the pancreas is described⁹⁶ in a 13 year old girl with a family history suggesting that other members had the same condition. The unusual part of the story was that the patient was well until 10 years of age except for severe winter colds. However, respiratory infections increased and after 4 admissions was the cause of death. Steatorrhea was also demonstrated. At postmortem there was complete atrophy of the pancreatic acinar tissue with intact islets, but no cystic changes. The liver was fatty and there was biliary cirrhosis. Another report⁵⁹ was unusual in that the patient died at 3 days of age with respiratory symptoms, but who at autopsy showed in addition to fibrosis of the pancreas, meconium ileus. A brother had had the same disease, but lived 4 months before death. The universal existence of cystic fibrosis of the pancreas is indicated by 2 cases from Canada described in French¹¹³ of two children with all of the characteristic clinical manifestations described so many times. One patient died at the age of 6 months and the other at the age of 16 months. Autopsy in one case showed the characteristic findings in the lungs and in the pancreas.

What seems to be the most promising therapeutic report⁶⁵ on cystic fibrosis of the pancreas is a study of 110 cases of which 40 were living at the time of the report. The surviving children are as old as 7 to 8 years. The diagnosis was confirmed, in all of the 40 cases who are doing well, by the persistent absence of duodenal tryptic activity. The important part of therapy was the necessity of maintaining good nutrition by giving at least 40 per cent more

than the normal caloric and 55 per cent of the normal protein requirements based upon the figures published by the National Research Council. They found that these patients would actually take this much food if given, and that the nutrition can be maintained with hyperalimentation provided the episodes of pulmonary infection are treated as they occur. The latter consisted merely of chemotherapy with or without aerosol penicillin and streptomycin. This rather simple approach to therapy in fibrocystic disease of the pancreas seems quite logical, and the results thus far seem most promising. Similar findings are reported in another paper¹⁰⁹ already discussed.

Cystic fibrosis of the pancreas of a kind was produced experimentally¹¹⁰ by the injection of physostigmine and pilocarpine in rats which produced definite vacuolization in the pancreas which was widespread. Of interest was the fact that atropine seems to neutralize this effect. The vacuoles contained no fat.

PANCREATIC CYSTS

Two types of pancreatic cysts have been described, not including the tiny cysts which were previously mentioned in cases of chronic pancreatitis. The most dramatic is the single large cyst filling and distending the lesser peritoneal cavity. In addition, a number of cases have been reported in which somewhat smaller cysts, either single or in the form of multiloculated cystadenomas were encountered and excised.

In a report¹²⁰ of 9 cases, a variety of lesions were found in which excision was carried out in 5, 2 of them followed by persistent fistulas. Simple marsupialization was effective in one case, and in 2 cases anastomosis between the cyst and the jejunum was carried out with satisfactory end results. In a series of 5 cases⁸ one exhibited an unusual complication in that the cyst ruptured into the colon with hemorrhage, sepsis and death. The other 4 were all operated upon and the cyst marsupialized; all finally ceased draining and completely healed at the time of discharge, although no follow-up studies were recorded. Two cases of pancreatic cyst⁹ were described in young men aged 20 and 21 years of age, who had had a crushing injury to the upper abdomen and chest. A cystic mass was observed 57 and 45 days afterwards, which enlarged rapidly. Operation revealed the cyst which was marsupialized and drainage ceased eventually and spontaneous closure occurred. Both cases curiously enough showed a left pleural effusion about 2 weeks after injury in spite of the absence of fractured ribs. A case of cystadenoma of the pancreas⁵³ was described in which operation was carried out because of abdominal pain and an epigastric mass. Although the preoperative diagnosis was mesenteric or omental tumor, a multiloculated cyst was found in the head of the pancreas which was completely excised; the patient remained well for a 2 year follow-up. An unusual case of pancreatic cyst⁹⁵ was described with a sudden acute onset developing spontaneously with swelling of the upper abdomen and dull epigastric pain. The swelling disappeared suddenly one day before admission and there followed a gradually increasing epigastric pain followed

by nausea and vomiting, and abdominal distension. At operation a cyst in the lesser peritoneal cavity was found which had ruptured into the abdominal cavity from which 1500 cc. of coffee-like fluid was aspirated; the fluid contained a high concentration of amylase. The cyst was drained and the postoperative course was uneventful for 12 days, when the pain recurred and the wound then discharged a large amount of fluid containing not only amylase but also lipase and trypsinogen. This discharge lasted for 10 days without evidence of wound digestion, but then closed; healing occurred and the patient remained asymptomatic for 9 months afterwards. A case is described² with what seems to be a definite history of acute pancreatitis, followed in 3 weeks by a characteristic pancreatic cyst which was drained at operation by marsupialization and packing. It healed finally after 27 days and the patient was followed for 2 years and was in fairly good health. Two cases of pancreatic cyst are reported⁸⁰ one of which seems to be a typical instance in which marsupialization was followed by persistent drainage, but in which 20 per cent silver nitrate solution was used to cauterize the cyst each day. On the 13th day drainage ceased, and the patient remained well.

The use of surgical procedures to anastomose with the gastrointestinal tract pancreatic cysts or the sinuses which remain after their drainage is receiving more attention. Thus, in one of 2 cases⁸¹ this procedure was done at the first operation, using a loop of jejunum which was anastomosed to the cyst, and an enteroenterostomy carried out below the loop. In the second case the patient had had a persistent draining fistula for 2 years following marsupialization. The stump of the fistula was anastomosed to a loop of jejunum with enteroenterostomy. No follow-up of these cases was mentioned.

In another case⁷¹ operation was performed in a patient who had had 3 attacks which appeared to be pancreatitis. The large extra-alimentary epigastric mass proved to be a pancreatic cyst and an anastomosis was made between it and a loop of jejunum prepared according to the Roux technic. Six weeks after operation the patient was asymptomatic and gaining weight with complete disappearance of the mass. Anastomosis between the pancreatic cyst and the stomach was carried out in one case²⁵ in which the first operation consisted of marsupialization which was satisfactory except for some difficulty due to the electrolyte balance and skin irritation following drainage. Healing occurred; however, 9 days after this operation a second mass was detected and jaundice developed and the abdomen was reexplored. A second cyst was found which was compressing the duodenum and common duct. This cyst was anastomosed to the stomach. The postoperative course was uneventful and follow-up to date revealed the patient to be asymptomatic.

Another case was recorded⁴⁷ in which the cyst was also anastomosed to the jejunum, using the Roux technic. However, the same author reported a second case in which simple external drainage was performed, and although this sinus persisted for 3 years, it finally closed. Two months after the sinus closed the patient developed symptoms of high intestinal obstruction. At operation a large, orange-sized epigastric mass was found which was excised and proved to be a recurrent cyst. The patient

remained asymptomatic for a follow-up period of one year. An unusual case was described⁷² in a patient who was operated upon for symptoms of pyloric obstruction which were due to a 12 x 17 cm. cyst extending from the tail of the pancreas to the duodenum; it was almost completely excised. The abdomen was closed and the patient had an uneventful recovery. The same author described another case in a patient who had a history of acute pancreatitis 2 years before the development of a typical epigastric mass which at operation proved to be a pancreatic cyst, which was drained. The sinus closed in 6 weeks.

Three interesting reports on pancreatic cyst come from Germany. In one,⁴⁶ following a complete review of the literature, 2 cases are described in which a retrocolic Roux type of anastomosis was carried out between the cyst and the jejunum. In the second case, the cyst was anastomosed to the posterior wall of the stomach also through the retrocolic approach, following an opening in the mesocolon. The follow-up was quite satisfactory in both cases up to 3 years in one, 6 months in the other. In the second report¹²⁷ a pancreatic cyst was found but because of dense adhesions could not be mobilized. The surgeon then opened the stomach by an incision in the anterior wall and from within the stomach, anastomosed the posterior wall to the cyst after evacuating it of several liters of fluid. The patient was a 20 year old girl. Follow-up revealed an excellent result for 15 months. At this time there was no roentgenological evidence of any abnormality after the usual barium meal. In the third report⁷⁴ a 58 year old woman is described in whom an anastomosis was made between a pancreatic cyst and the duodenum, and who died of carcinoma of the rectum 6 years later. At autopsy there was no evidence whatever of pancreatic cyst or of its anastomosis to the duodenum with the exception of a tiny scar. The pancreas seemed perfectly normal in size, shape and consistency.

Practically all pancreatic cysts appear in adults, but one was described in a 6 months old infant⁶⁸ in whom an abdominal mass was felt in the left side of the abdomen. Radiologic study showed evidence of gastrointestinal displacement. After an upper respiratory infection subsided, operation was carried out and a large cyst 16 cm. in diameter was found and removed in toto, including a portion of the body of the pancreas. The cyst had no epithelial lining and contained one liter of fluid which had a high concentration of amylase. Fibrotic pancreatic tissue was discovered in the wall of the cyst by microscopic examination. Biopsy of the remaining pancreas showed fibrosis and lymphocytic infiltration. There was no history of trauma. The post-operative course was uneventful and 2 months later the baby was well and its weight was normal, without upper respiratory infection or dietary difficulties which might be expected if this patient were actually suffering from a cystic fibrosis of the pancreas.

PANCREATIC SECRETION

The effect of resection of the pancreas on pancreatic function was carefully studied^{125, 126} in 10 cases at significant intervals after operation. It was established that even though there might be large losses of nitrogen in the feces, nitrogen balance was not difficult to achieve even on a moderate intake of 60

grams per day. However, the use of pancreatin definitely increased the amount of protein utilized. This was even more striking in the case of fat, which in every case showed a greater absorption following the ingestion of 15 grams of pancreatin a day in 3 doses of 5 grams each in enteric coated capsules. These cases were followed for from 2 to 3 years, and 7 out of 10 were living, 4 of them in good health, and 8 out of 10 were able to gain weight or maintain satisfactory weight on a high protein, high carbohydrate and low fat, high caloric diet with pancreatin, although two patients were somewhat handicapped by diarrhea. A meticulous study³³ was carried out of the total fecal solids in the cases of chronic relapsing pancreatitis already referred to.⁴³ All patients were on carefully controlled diets consisting of 100 grams of fat, 270 grams of carbohydrate and 117 grams of protein with a caloric value of 2400. The feces were carefully measured between two carmine markers. Ten of the patients had and 10 did not have diabetes. The diabetics all showed evidence of calcification, and 7 of them had gross steatorrhea; they averaged 53 grams of fecal solids as compared with 27 and 25 in the control group and in the group without diabetes. Confirming this increase in solids was the increase in total fat, 21 grams as compared with 4, the per cent of absorption of ingested fat, 21 per cent in comparison with 4 per cent. The total amount of nitrogen excreted was 3.2 grams as compared with 1.5 for the controls. The percentage of the ingested nitrogen which was lost was 17 as compared with 8 per cent. In general, the fecal losses roughly were proportional to the degree of damage to the pancreas. It must be emphasized that these figures were averages and that there was considerable variation between the individual cases. Thus in only 5 of the 10 patients with diabetes and steatorrhea did the total fecal solids exceed the normal upper limit. These findings show that the appearance of gross steatorrhea is not necessarily of quantitative value as far as estimating the degree of pancreatic insufficiency.

The role of pancreatic secretion in peptic ulcer formation was studied in dogs.⁸⁷ Histamine in beeswax was used as the provocative agents for peptic ulcer. In 4 controls no ulceration was produced; however, in 4 animals following total pancreatectomy, in 4 following ligation of both pancreatic ducts, all developed peptic ulcers with bleeding or perforation, the latter causing death in 6 out of the 8 experiments. On the other hand, when diabetes was produced by giving alloxan in 4 dogs, only one developed a large perforated duodenal ulcer. The inference seems justified that interruption of pancreatic secretion into the duodenum makes possible duodenal ulceration from histamine in wax. That this experimental evidence may explain the clinical occurrence of peptic ulcer is shown by a report⁷⁷ of 3 patients in whom a peptic ulcer followed total or partial pancreatectomy. In one case the ulcer led to a fatal peritonitis 4 months after resection. In the second case the patient died in 6

weeks from recurrence of carcinoma, but a definite gastric ulcer of the lesser curvature was found at autopsy. In the third case the patient developed definite peptic ulcer symptoms one month after resection, even though no definite x-ray finding was demonstrable. The symptoms responded to diet.

A decrease in pancreatic function in malnourished infants deprived of protein was indicated in a brief report¹¹² in which duodenal aspiration revealed a practical absence of pancreatic secretion. This returned to normal, however, when protein as milk was given to the infant in adequate quantities. Upon discontinuing the milk the enzymes disappeared. Study of pancreatic function in infancy was made¹²² by examining the secretions in the pancreatic ducts as well as by histological study of the pancreas itself in 19 full term infants dying of various causes, as compared with the same observations made in premature infants. In the premature infants very few pancreatic zymogen granules were found, whereas they were abundant at full term, though they appeared to vary with the weight of the individual.

A number of studies were made on pancreatic secretion in dogs. In one of these studies¹¹⁷ constant intravenous injections were made with a cannula in the pancreatic duct for the collection of secretion. Secretin produced no stimulant effect on the production of amylase or alkaline phosphatase, although the volume increased. On the other hand, pancreozymin caused a three to four-fold increase in amylase production without change in alkaline phosphatase. In a rather complicated experiment⁶⁴ evidence was obtained which was interpreted to mean that there was no correlation between the acidity of the duodenum and the secretion of pancreatic juice.

The possibility of influencing the enzyme content of the pancreas was shown²² by experiments in which chickens were fed raw soy bean diets. They failed to gain weight and showed a large pancreas whose proteolytic activity showed an increased value as compared with control animals fed autoclaved soy beans. The addition of 0.5 per cent methionine to the raw soy bean diet produced normal growth but the high ratio of pancreas size to body weight persisted as did the increased proteolytic activity in the pancreas. The difference in the two groups was striking. Purification and crystallization of human amylase was carried out⁶⁹ and showed the same solubility and the same degree of activity when the amylase was obtained from either the saliva or the pancreatic juice. Crystalline amylase of pork origin, on the other hand, had a lower activity but a higher solubility. An interesting protein was isolated in crystalline form from the pancreas⁵⁶ which was a trypsin inhibitor, having anticoagulant properties. One may speculate as to its possible role if absent in the thrombophilia so often seen in carcinoma of the pancreas.

Further data has appeared⁴⁵ on a rapid method for the determination of lipase requiring incubation for only one hour at 37° C. The normal range (85

to 205 lipase units) is somewhat wider than that which applies to the amylase test, which is between 80 and 120.

Lipotropic Factor.—Investigations in regard to the presence of a lipotropic factor in the pancreas continue. The ability of this factor to lower the fat content of the depancreatized dog liver by as much as 20 per cent with return to normal in 48 to 124 hours has been described⁵⁸ by a new term lipodieresis. Lipocaiac produced lipodieresis as shown previously, but was less efficient than a glycerine-water extract of pancreas. On the other hand, a study of the lipotropic activity of pancreatic extracts on fatty livers produced by dietary means showed¹⁶ that lipocaiac was the most efficient, yielding a total fatty acid content of the liver after 20 days in rats of 3.8 per cent as compared with the two other extracts which gave values of 15.4 and 15.8 per cent. The influence of lipocaiac on the changes produced by complete pancreatic obstruction was studied in 10 dogs¹⁷ and found to be preventative as well as corrective within 2 or 3 days except for the fall in the prothrombin level which was not influenced. (The corrective influence was studied 58, 112 and 161 days after obstruction and proved more effective the earlier it was begun, although the response was never quite complete. Casein hydrolysate corrected both the hypoprothrombinemia as well as the hypoproteinemia. Of special interest was the fatty infiltration of the liver which could be prevented by the administration of extract equivalent to 75 grams of fresh pancreas.

Secretin.—Secretin was extracted from the upper gastrointestinal tract³ in 17 out of 18 adults as well as in 13 children coming to autopsy for various reasons. Secretin activity was measured by the response in a dog with pancreatic fistula. Premature or new born infants showed a low secretin activity. In one patient with fibrocystic disease of the pancreas, dying at 16 months of age, extract proved to be very weak in secretin activity. The author believes that there is an inadequate production of secretin in fibrocystic disease of the pancreas, but further proof will be required before this theory can be substantiated. A study of the duodenal contents obtained before and after the injection of secretin was carried out in a large series of cases,³⁴ 28 of them with chronic pancreatitis, the diagnosis being made in 16 by x-ray evidence of calcification and/or fatty stools and by surgical exploration. In comparison with 20 normal subjects, definite differences were obtained in volume, total bicarbonate, amylase, trypsin and lipase. However, the variations in both groups were so great that there was a considerable overlap. To illustrate, the average total bicarbonate values were perhaps the most strikingly different. Yet the controls varied between 3.5 and 17.75, whereas those with pancreatitis varied from 0.5 to 14.2 total millimols excreted in a 40 minute collection period. The authors compared these observations with the findings on fecal excretion and found that the results agreed in 7 cases, whereas in 4 cases the secretin test was

positive or the fecal excretion test was negative. In 3 cases there was no defect demonstrable with either test.

Amylase.—A colorimetric method for the determination of amylase is described,⁶² the values of which ranged from 9.2 to 34.9 in normals, which is a considerably wider variation than that obtained with the customary methods. A comparison of amylase and lipase was made¹¹⁸ in 10 cases of acute pancreatitis, diagnosis being made by operation in 9. It was found that the values for each test were parallel both in the degree of elevation and subsidence to normal, although considerable individual variation was present. A study was made of the serum lipase following pancreatic duct ligation and pancreatectomy.⁷⁶ Following ligation the lipase began to rise, although there was much variation, e.g., in 2 dogs the highest values were reached on the 10th and the 22nd days following ligation of ducts. In 3 dogs, after pancreatectomy, there was a steady decrease until death, which occurred 5 to 6 days later in all cases. When pancreatectomy was performed 5 days after ligation of the ducts, there was an immediate drop in the elevated lipase so that by the second day the value was almost zero in 3 cases, but still present in 2. A pancreatic fistula produced after ligation of the duct was followed by a decrease in blood lipase immediately.

MISCELLANEOUS

A case of annular pancreas was described¹² in a 53 year old female who 3 weeks before had had a cholecystectomy and exploration of the common duct. Because of recurrent pain and hematemesis, she was operated upon again and the annular pancreas found, which was sectioned. The patient had a stormy postoperative course including drainage of a right phrenic abscess, which was followed by duodenal fistula; a gastroenterostomy, done on the 26th postoperative day, was followed by a fatal outcome 2 days later. At postmortem the pancreas itself proved normal microscopically. A case of aberrant pancreas³² was reported in a 13 year old female who had had an uneventful appendectomy for acute appendicitis 6 months previously. Intestinal obstruction developed and at operation an abscess containing 10 cc. of pus was found, involving the ileum at a point of perforation. This exhibited a tiny nubbin of tissue which was removed and the perforation closed. Sections revealed pancreatic tissue attached to the ileal wall.

A review of traumatic rupture of the pancreas included a case report⁴⁸ of a 6½ year old female who was struck by an automobile but experienced no symptoms until the next morning when she was admitted with evidence of severe abdominal pain, nausea and vomiting. She was operated upon 48 hours after the accident with a diagnosis of laceration of the spleen, but at operation extensive omental fat necrosis and 1500 cc. of brownish colored peritoneal fluid were found. There was a vertical tear across the tail of the pancreas with a jagged opening 3.5 cm. long. It was treated by drainage only. The patient had a long postoperative course, but was discharged in 2½ months and remained well for 7 years afterwards. Another case of rupture of the pancreas

was described⁶² in a 35 year old male who sustained a crushing upper abdominal injury one hour before admission. The amylase value was high and because of persistent symptoms the patient was operated upon 48 hours later and extensive abdominal fat necrosis was found. The head and body of the pancreas was edematous and hemorrhagic, but there was no loss of continuity. Nothing further was done and the abdomen was closed. The postoperative course was uneventful and the patient was asymptomatic two months later. The amylase gradually returned to normal in one month.

Still another instance of acute rupture of the pancreas was described¹ in an 18 year old male who sustained a blunt trauma to the upper abdomen and was operated upon one hour later. Free blood was found in the lesser sac. A vertical tear in the mid pancreas to the left of the vertebra was found which was sutured with catgut and the abdomen closed with drainage. The patient continued to have pain referred to the pancreatic area for 3 or 4 days, which subsided. Recovery was complete and the patient remained asymptomatic for a 2 year follow-up.

Metabolic studies following total pancreatectomy were reported in 3 cases⁴⁰ which are of interest in this review because blood lipase and amylase were normal long after removal of the pancreas (40 weeks) in one case. In another case no blood amylase was found at the 13th week, but lipase was present. No evidence was found of deficiency in the lipotropic factor in two cases coming to postmortem.

Cholangiograms are shown¹⁰⁵ of a patient after cholecystectomy in which the pancreatic duct was visualized as joining the lower end of the common duct; nevertheless a later film showed that it had emptied independently of the common duct. This was presented as evidence of the ability of the pancreatic and common ducts to empty independently, even though they had a common opening into the duodenum.

Variations in the blood supply to the pancreas of considerable interest were described⁷⁰ based upon 200 human dissections. There was considerable constancy of 4 arteries to the pancreas, called retroperitoneal, supraduodenal, the dorsal pancreatic and the transverse pancreatic, not usually described by these terms. A method for the experimental production of a pancreatic fistula was described⁷ utilizing a stainless steel apparatus, permitting at will the collection of pancreatic juice or its diversion into the intestine.

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THEPHORIN (PHENINDAMINE) IN THE TREATMENT OF GASTROINTESTINAL ALLERGY*

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In 1946, a study¹ of intraluminal jejunal pressure in intestinal allergy was undertaken using a balloon-tipped Miller-Abbott tube for the transmission of the pressure to a diaphragm-capped chamber from which a stylus recorded a tracing on kymograph. A T-tube inserted into the transmitting system was connected to a water monometer in order to correlate the pressures read in c.c. of water with the variations in amplitude of the kymographic tracings. Patterns were obtained for the fasting state of the jejunal segment and for the alterations of amplitude and rhythm following the intratubal introduction directly into the intestinal lumen of inert or non-allergic substances such as water, normal saline solution and 5 per cent glucose solution. Study was then extended to the use of similar volumes of solutions or suspensions of sample foodstuffs to which the subject, on clinical observation, did not appear to be allergic. Finally, the effect of suspected allergenic foods was investigated. In all studies the balloon was situated in the same position with relation to the ligament of Treitz, as observed fluoroscopically.

In this manner it was reasonably established that certain foods, presumably allergenic, could elicit a significant change in intrajejunal pressure and its rhythmic fluctuations, and that these changes occurred independently of the simple distensive effect of water, the inclusion of sodium chloride or glucose, and the chemical or hormonal activities involved in the introduction of a foodstuff per se. Admittedly, the method employed does not approach the accuracy of measurement of intraluminal pressures or the fine definition of their fluctuations which have been secured by the more intricate mechanisms devised by Abbott and his associates² or by Brody and Quigley³. However, the alterations and amplitude of the phasic pressure waves as observed with this apparatus have been of an order sufficient to render them significant. Furthermore, these changes were most often accompanied by subjective manifestations which the patient identified with the symptoms he commonly suffered following ingestion of the same foods. When kymographic records typical of reaction to one or more food allergens were obtained in individuals who complained of gastrointestinal symptoms after eating the same foods, and who became symptom-free during the total dietary exclusion of those foods, it was felt that a true digestive allergy had been demonstrated. In the course of that investigation,

* Harvard kymograph and Thephorin used in these studies generously supplied by Hoffmann-La Roche.

now being continued, the effect of certain therapeutic agents was also observed. Among these were ephedrine, specific food propeptans¹ and some of the antihistaminic preparations in current use. It was found that ephedrine, administered orally or transtubally, in the dosage of $\frac{3}{8}$ or $\frac{3}{4}$ grain, thirty minutes before or concomitantly with the instillation of a recognized allergen, produced no significant alteration of the positive kymographic pattern in the two patients studied. Inasmuch as the predominant action of this substance is vasoconstrictive, it was not to be expected that any alteration would occur in a state in which increased muscle tonus and arrhythmia appear to be major components.

The administration of specific propeptans forty five minutes before the instillation of allergenic foods in five cases brought out highly interesting but inconclusive results. In one patient the tracing revealed no evidence of the marked arrhythmicity and heightened intraluminal pressure which had appeared following the use of the same allergenic food one week earlier. This patient subsequently responded satisfactorily to clinical propeptan desensitization. Two cases demonstrated slight diminution in amplitude of the tracing but little change in arrhythmicity; both patients complained of cramps and distention similar to that felt during the original observation. The other two cases showed no change in tracing or in symptomatology.

Because of the notable changes induced in the intestinal rhythm and intraluminal pressure by the introduction of allergenic foods, the possibility of modification by antihistaminics was next investigated. In vitro studies by Lehmann,⁵ Mayer,⁶ Halpern⁷ and others have demonstrated the efficacy of Benadryl, Antergan, Neoantergan, Pyribenzamine and Thephorin in preventing the histamine contraction of isolated strips of guinea pig intestine. In a review of antihistaminics in 1947, Pfeiffer and Loew⁸ commented on the phenomenon that although certain of the preparations themselves tended to induce contraction of intestinal muscle strips, each drug displayed demonstrable antagonism to the spasmogenic action of histamine. Hoekstra and Steggerda⁹ found similar blockage of histamine-induced intestinal spasm, in vivo, in dogs so prepared that the colon had been rendered opaque to X-rays by thorium dioxide; concurrently with radiologic observation, pressure changes were recorded by means of an open-tipped catheter inserted into the colon per rectum.

The mechanism of such anti-spasmogenic activity in these compounds has not been demonstrated conclusively. Apparently each preparation combines, in varying proportions, myotropic spasmolytic, histaminolytic and atropine-like properties, interfering both in the cholinergic and histaminic systems.¹⁰ Whereas Pyribenzamine is predominantly antihistaminic, Thephorin and Benadryl partake of both activities.⁵ Despite the experimental indication of anti-spasmogenic function by various preparations, reports of their clinical trial in food allergy have been meager and inconclusive. Feinberg¹¹ has found

indication of benefit from the use of Pyribenzamine in acute gastrointestinal upsets due to food allergy, and McGavack^{12, 13} and others have reported isolated instances, but the field has not been explored extensively.

The antihistaminic preparation employed in this phase of the study was Thephorin (phenindamine, Hoffmann-La Roche), a pyridindine derivative in contrast to the ethylene-diamine and other groups which have been synthesized for the same purpose. Investigations of its toxicity^{14, 15} indicate that, weight-for-weight, it is less apt to produce untoward manifestations than Benadryl and Pyribenzamine. Such effects as do occur are generally stimulating in character (insomnia, apprehensiveness) and may be controlled readily by small doses of phenobarbital. Insomnia, in particular, tends to decrease or disappear with continuation of therapy.

In intubation studies in which Thephorin was employed, a single dose of 25 mg. was administered orally one half hour prior to the intrajejunal instillation of a known food allergen, one to two weeks after an initial intubation procedure had demonstrated the specificity of the allergen. Eight cases have been so studied in addition to one, reported elsewhere, in which the procedure was carried out during a period of treatment with Thephorin. Figure 1 represents segments of the tracings obtained in the case of J. W.

The upper strip represents the kymographic recording obtained in the fasting jejunum. The middle tracing was inscribed six minutes after the intrajejunal instillation of 10 c.c. of milk during the same intubation. One week later the patient was again intubated, the position of the tube was verified fluoroscopically, and the patient was given 25 mg. of Thephorin orally. One-half hour later, 10 c.c. of milk was again instilled into the jejunum. The lower series of tracings consists of segments made at intervals of two minutes for twelve minutes. The kymograph was kept in operation for a total of 30 minutes, but no additional changes were noted. In the remaining seven cases, similar results were achieved in five. These included three instances of sensitivity to milk, one to egg albumin, and one to wheat. In each study the amplitude and rhythm of the phasic pressure waves were not appreciably altered by the instillation of the respective allergenic food after a single 25 mg. dose of Thephorin. The quantity of allergenic food so administered is admittedly small, but it had been sufficient to evoke a significant response in each case during a prior intubation. In the two patients in whom Thephorin had no obvious effect on the reactivity to specific foods, one was sensitive to port, the other to milk. In both cases, the abnormal rhythm and intraluminal pressure elicited by the introduction of the allergen alone showed no alteration after the oral administration of 25 mg. of Thephorin. It should be noted here that these two latter patients complained of the same subjective symptoms during their phases of reactivity as they commonly suffered upon eating the foods. On the other hand, the six

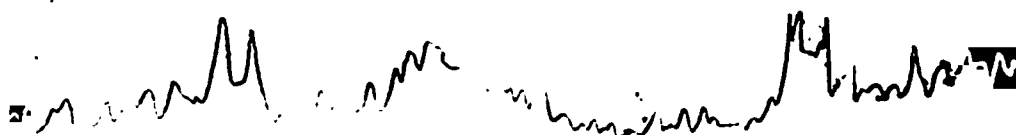
patients in whom the kymographic tracings remained within normal limits after the use of Thephorin displayed no symptomatic abnormality during the intubation in which the drug was employed.

In addition to the eight cases studied by intubation, thirty-three other patients were determined to have gastrointestinal food allergy by other methods of study.

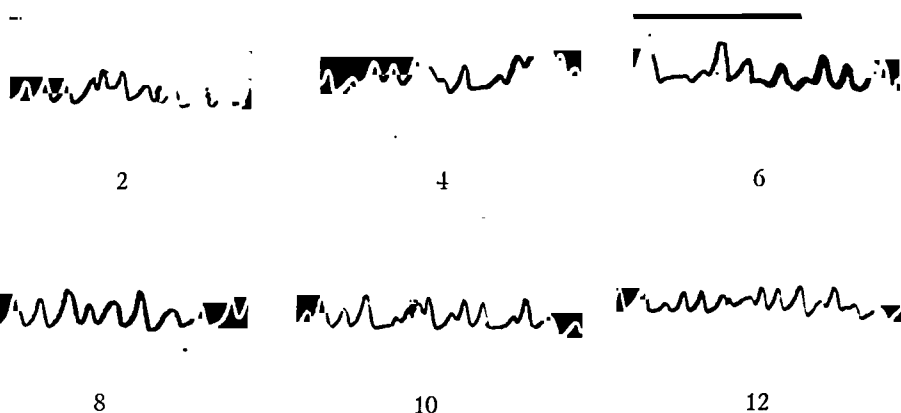
FIG. 1



First jejunal intubation—Fasting state



Same tracing—6 minutes after instillation of milk 10 c.c.



Second intubation—segments of tracing at 2-minute intervals following instillation of milk, preceded by Thephorin 25 mg. orally 30 minutes before.

In most instances a detailed history suggested the possibility of such an entity and often indicted a single food or a group of foodstuffs. A gross illustration would be that of the individual who had had infantile eczema which subsided during childhood and who, in adult life, developed an ulcer-like syndrome which was exacerbated by intensive application of a Sippy diet. In all cases, gastrointestinal X-ray series, sigmoidoscopy and, where indicated, cholecystography were performed and found negative for the presence of organic disease which could be responsible for the symp-

tomatology. In thirty-three patients the diagnosis was based upon the results of various modifications of the Rowe elimination diets. In eight patients whose outstanding complaint was diarrhea, the method described by Thomas and Renshaw¹⁶ was applied. This consists of the sigmoidoscopic or proctoscopic observation of erythema, edema, vascular engorgement or hemorrhage produced by the application of an allergenic substance to the surface of the rectal mucosa. In all such instances the observations may be controlled by the similar application of non-allergens during the same instrumentation. When the diagnosis of food allergy had been made and the suspected food or foods investigated, Thephorin was prescribed in a dosage of 25 mg., three or four times daily. Because of the possibility of insomnia as a side-effect of the preparation, any administration after 7 P. M. was accompanied by the use of phenobarbital $\frac{1}{2}$ grain or Presidin (Roche) 100 to 200 mg. The diet was arranged to include the specifically allergenic foods in small quantities at least twice daily; in cases in which the patient remained symptom-free the quantities were then gradually increased to amounts normally consumed. At irregular intervals Thephorin was withdrawn and tablets of similar appearance substituted, or all medication suspended. During both such phases continued ingestion of the allergenic foods was followed by reappearance of the patients's symptomatology within 24 to 72 hours. Such recurrence was of the same type and generally of the same severity as that suffered prior to therapy. The medication was administered either before or after meals. Lehmann⁵, in studies of anti-histaminic potency on isolated guinea pig intestine, demonstrated an increasing effect of Thephorin with increase in the time interval between the application of the anti-spasmodic and the spasmogenic agents. Although the time interval involved in his work was necessarily brief, it was considered of significance; taken together with the observed interval necessary for symptom relief by Thephorin in respiratory allergy, a schedule for the present study was established. In patients whose symptoms appeared within 30 minutes after food, the drug was given before meals; in those whose symptoms occurred later than 30 minutes after food or had no apparent relation to the time of ingestion of food, the medication was administered after meals and at bedtime.

The majority of the patients in this study presented more than a single gastrointestinal symptom,—usually two or three. For example, post-prandial mid-abdominal pain and fullness and nausea frequently constituted the initial complaint. Since the effect of presently known anti histaminics is recognized to be entirely palliative, their clinical evaluation is largely determined by the relief of symptoms. Chart I represents an analysis of the symptom response in the 41 cases of this series. Unfortunately, there were but four patients who exhibited vomiting and three who presented the symptom of substernal distress; in these two groups, each too small to warrant valid conclusions, the effectiveness of Thephorin was poor. Other symptom groups, comprising 7 to 23 patients each, gave evidence of generally good response to Thephorin. This was most notable, as might be expected from the studies of intraluminal jejunal pressure changes, in symptoms due to abnormal intestinal tonus or aberration of motility. In particular, the group of 23 cases of diarrhea displayed complete relief in 18 patients and partial amelioration in two others. Seven of the 11

patients who complained of nausea reported full relief and two additional ones had definite improvement. In those patients who presented mid-abdominal pain and sensations of abdominal fullness, the two complaints usually occurred together and at the same time. Similarly, the degree of symptomatic relief of these groups was roughly parallel. In the patients whose pain and/or fullness occurred within one-half hour after meals, pain was abolished in 44 percent and decreased in an additional 25 percent; fullness was abolished in 50 percent and reduced in another 17 percent. Figures for pain and fullness occurring more than one-half hour after meals were also parallel. In these groups as a whole, the maximum benefit was reported by patients whose mid-abdominal symptoms began from one-half to two hours after food; pain was wholly or partially abolished in 86 percent and fullness in 85 percent. The remaining symptoms presented in this series, heartburn and belching, did not appear to be affected by the administration of phenindamine in the dosages employed.

CHART 1

Symptom Response to Administration of Phenindamine in 41 Cases of Gastrointestinal Allergy

	NO. CASES PRE- SENT- ING SYM- TOMS	COMPLETE RELIEF		PARTIAL RELIEF		NO CHANGE	
		Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent
Abdominal pain.....	33	18	55	8	24	7	21
0 to 30 minutes after food.....	16	7	44	4	25	5	31
30 to 120 minutes after food.....	7	5	72	1	14	1	14
120 minutes or more after food.....	10	6	60	3	30	1	10
Abdominal fullness.....	29	17	58	5	18	7	24
0 to 30 minutes after food.....	12	6	50	2	17	4	33
30 to 120 minutes after food.....	13	9	70	2	15	2	15
120 minutes or more after food.....	4	2	50	1	25	1	25
Nausea.....	11	7	64	2	18	2	18
Vomiting.....	4	1	25	1	25	2	50
Diarrhea.....	23	18	79	2	8	3	13
Heartburn.....	12	3	25	4	33	5	42
Belching.....	11	4	36	4	36	3	28
Substernal distress.....	3	1	33	0	0	2	67

In the group of 41 patients as a whole, there were some 126 individual symptoms described. Of these, 69 were completely relieved and 26 partially relieved, —a total of 75 per cent symptom amelioration. Thephorin appears, therefore, to be of significant value in the symptomatic therapy of gastrointestinal food allergy. It is to be emphasized that its effectiveness is limited to the period of its immediate physiological action in the body and that, in common with other anti histaminics, it is not to be employed with a view to permanent cure. In 1947 it was the impression of Feinberg¹⁷ that the antihistaminics "may help or prevent such manifestations (of gastrointestinal allergy) but not in all instances by any means." The series here reported serves to confirm and amplify the preventive action of the antihistaminic used, Thephorin. It also points up the observation that symptoms may not be prevented in every instance, at

least, not in the doses here employed. There is, however, sufficient evidence to warrant its application in certain circumstances.

There are two phases of the treatment of gastrointestinal food allergy in which phenindamine has been found to have particular value in the present group. Patients whose specific food allergens have been isolated and whose symptomatic response to the antihistaminic has been good, may readily be maintained on such therapy during the initial stages of desensitization. Such palliative administration of phenindamine does not appear to interfere with the process of desensitization of food allergy. Analogous observations have been made in use of various antihistaminics during the definitive treatment of respiratory and dermatological allergies. In many cases, however, food sensitivities may be multiple and desensitization therapy unsuccessful or impracticable. Such cases represent another group in which the palliative effect of phenindamine may be found desirable and valuable. Because of its high rate of symptom relief when used therapeutically, Thephorin can be employed to serve in yet another capacity, that of a guide to the diagnosis of gastrointestinal food allergy generally. In the absence of clinical, roentgenographic and laboratory evidence of organic digestive disease, the trial administration of phenindamine often induces amelioration of symptoms to such a degree that attention may be focused upon an allergic etiology, and methods of specific food investigation may be begun. The possibility of error due to the 25 per cent failure of symptom relief in the present series cannot be overlooked; further study is now under way to determine the importance of hypersecretion and hypermotility in cases which have shown failure of symptom response to Thephorin.

SUMMARY

The efficacy of Thephorin (phenindamine) in the symptomatic treatment of gastrointestinal food allergy has been studied in 41 patients exhibiting a total of 126 complaints referable to the digestive tract. Complete relief was obtained in 69 symptoms and partial relief in 26 more; thus, relief or amelioration was obtained in 75 per cent of complaints. Of the 41 patients, most of whom presented multiple complaints; 26 (63 per cent) obtained complete relief. The diagnosis of food allergy was based upon intubation studies, elimination diets, proctoscopic observation, or combinations of these methods. As in the employment of antihistaminics for other forms of allergy, such therapy is symptomatic, not curative. However, Thephorin appears to be of significant value in (a) symptom control during the procedure of specific desensitization (with which it does not seem to interfere), (b) in palliation of symptoms in cases in which desensitization is impracticable, and (c) in the crude delineation of gastrointestinal allergy in patients who have no discoverable evidence of organic digestive disease and in whom differentiation from functional and neuropsychiatric

factors is indicated. It is possible that the combination of antihistaminic and anti-cholinergic effects of Thephorin, as evidenced in animal studies, has been responsible for the efficacy in symptom relief observed in this series.

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GASTRITIS IN THE DYSPEPTIC*

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This is a report of the gastroscopic findings in patients with complaints referable to the upper gastrointestinal tract. It deals primarily with those having normal roentgenographic studies of stomach and duodenum, and secondarily with those having duodenal ulcer.

Careful histopathologic investigations indicate a close correlation between gastroscopic diagnosis of gastritis and the pathologic findings. Schindler⁹ states: "In every case in which gastritis was diagnosed gastroscopically, histologic evidence of marked gastritis was also found." This has been substantiated by Benedict and Mallory.¹ Many writers still feel that gastritis is not a disease entity. Wolf and Wolff¹⁰ found changes in "Tom's" gastric mucosa which simulated all the types of gastritis described by Schindler^{7, 9} except the blood vessel pattern of the atrophied mucosa. It seems logical to attribute symptoms referable to the upper gastrointestinal tract to gastritis when it is present and no other lesions are demonstrable.⁶ Mild degrees of gastritis, however, may not produce symptoms.

The vast majority of cases of gastritis can be diagnosed only by endoscopy.⁹ The incidence of gastritis reported in consecutive endoscopic examinations varies in different series. Flexner and Fleishman⁴ reported 59.8 per cent in 256 examinations, Carey² 44 per cent in 700, and Schindler⁸ 41.8 per cent in 1,000 cases. A careful study⁵ of gastritis, duodenal ulcer and psychoneurosis conducted on navy personnel revealed gastritis and psychoneurosis uncommon in 23 patients with duodenal ulcer; but in 22 patients without ulcer, psychoneurosis of some degree was present in nearly 80 per cent and gastritis in nearly 50 per cent.

RESULTS OF THIS STUDY

We studied 286 individuals gastroscopically. This group was divided into two series: 173 were thought to have disease of the upper gastrointestinal tract although roentgenograms of the stomach and duodenum were normal, and 113 had duodenal ulcer. Age of the patients varied from 20 to 75, and all were males.

Of the 173 cases without ulcer, 131 (76%) had normal appearing mucosa, and 42 (24%) had gastritis. Thirty-five patients had superficial gastritis, of

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which 23 were mild to moderate and 12 were severe or moderately severe. Four had atrophic gastritis; 1 had superficial and atrophic gastritis; 1 had edema; 1 had hyperemia.

Of the 113 cases with proved duodenal ulcer, 93 (82%) had normal appearing mucosa, and 16 (14%) had gastritis. Twelve patients had superficial gastritis, 6 of which were severe and associated with some degree of retention, and 6 were mild to moderate. Two had hypertrophic gastritis; 1 had atrophic gastritis, 1 had edema. Four patients had associated gastric ulcers without gastritis.

TABLE I

	CASES	X-RAY FINDINGS	GASTROSCOPIC FINDINGS	
			Normal	Gastritis
Group 1.....	173	Normal	131 (75%)	42
Group 2.....	113	Duodenal ulcer	93 (82%)	16*

TABLE II

	SUPERFICIAL GASTRITIS		ATROPHIC GASTRITIS	HYPER-TROPHIC GASTRITIS	OTHER	TOTAL
	Moderate	Severe				
Group 1.....	23	12	4	0	3	42
Group 2.....	6	6†	1	2	1	16*

* Four cases not included had associated gastric ulcer without gastritis.

† Associated with obstruction and gastric retention.

COMMENTS

Our findings differed greatly from those reported in other series.^{3, 5} Gastritis was an infrequent finding generally, and particularly in the 173 cases of functional disorder. Furthermore, in a total of 600 consecutive gastroscopic examinations, including the 286 reported here, gastritis was found in less than 20 per cent.

There was no discernible symptom pattern that correlated well with the mucosal aberrations. Distress after meals, boring epigastric pain, nausea, burning, and the other familiar symptoms were encountered with monotonous regularity. Tests of gallbladder, pancreas and liver function done in many of these patients were found to be uniformly negative. Disease of the gallbladder and liver were no more common in the group with gastritis than in the group with normal mucosa. Patients having gastritis alone responded as well to the ulcer regimen as did those with ulcer. Special psychiatric therapy was not employed.

Minor traumata (passage of Ewald tube and lavage) did not affect the appearance of the mucosa.

CONCLUSIONS

The endoscopic findings in 173 cases of dyspepsia with negative roentgenographic studies are presented.

Forty-two (25%) showed abnormal gastric mucosa, the majority of these (76%) having only mild or moderate superficial gastritis.

In a group of 113 cases of proved duodenal ulcer even fewer cases of gastritis were found (18%).

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MODIFIED MANN-WILLIAMSON OPERATION FOR ENDOSCOPIC OBSERVATIONS OF THE ULCER BEARING AREAS*†

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The utilization of the intussuscepted conical valve principle in small bowel surgery permits a useful modification of the Mann-Williamson operation as it is employed in experimental peptic ulcer work.

With a properly constructed and well placed non-leaking valve, the area of the gastrojejunostomy where the ulcers develop can be brought under endoscopic observation, samples of gastrojejunal contents may be easily obtained by aspiration, and other time consuming procedures of securing data are simplified. Consequently, the result is a broader scope of investigation, and a more economical utilization of every individual experimental animal.

One begins the operation in the usual manner: First, the pylorus is divided and the duodenal stump inverted and securely closed. Then, the jejunum is divided close to the ligament of Treitz, and its proximal sectioned end is anastomosed with the lower ileum. Now, instead of the conventional end to end anastomosis between the distal cut end of the jejunum and the pyloric end of the stomach, a terminolateral gastrojejunostomy is made, leaving a 4 to 5 inch long jejunal stump above the anastomosis.

Into this jejunal stump an intussuscepted, leak-proof conical valve is constructed with the following steps:

(a) About $1\frac{1}{2}$ to 2 inches above the gastrojejunostomy, the jejunal stump is inverted in a ring-like fashion with a row of interrupted, sero-muscular silk mattress sutures.

(b) A second row of mattress sutures is placed over the first row in such a manner, that every stitch picks up the sero-muscularis $\frac{1}{4}$ inch on the anastomosis side, and 1 inch on the side of the free end of the jejunal stump. (Fig. 1.) When these sutures are tied, they invaginate the previously inverted circular fold of the intestinal wall toward the side where the shorter bite was taken; that is, toward the anastomosis.

This invaginated or intussuscepted segment of the bowel should be approximately $\frac{3}{4}$ to 1 inch long to be functionally effective. If necessary, a third row of interrupted mattress sutures may be placed in the same manner as the second row was made, in order to construct the optimal length of the valve.

* The facilities of the Animal Hospital of the Professional Colleges of the University of Illinois were made available for this work through the courtesy of Dr. George E. Wakerlin, Head of the Department of Physiology.

† I wish to express my appreciation to Donald L. Grieme, B.S. for his valuable assistance in connection with this work.

Through a stab incision, the free end of the jejunal stump is brought outside of the abdomen so that the bulging part, where the valve is located, is pulled against the peritoneum. At the level of emergence, the stump should be secured to the skin with a few stitches.

In larger animals, because of the larger lumen of the gut, the formation of the above described intussuscepted valve is simpler, and one can employ the same technic as in the human¹.

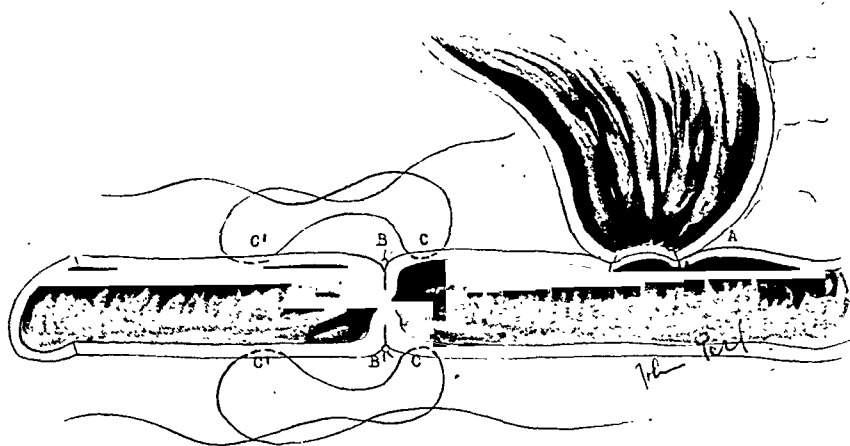


FIG. 1. Formation of the intussuscepted valve. Diagrammatic sagittal section of the site of the gastrojejunostomy and the jejunal stump.

A: Termino-lateral gastrojejunostomy.

B: First row of mattress sutures invert a circular fold of the bowel wall.

A second row of mattress sutures is placed over the first row in such a manner, that every stitch picks up the seromuscularis $\frac{1}{4}$ inch on the gastrojejunostomy side (C), and about 1 inch on the side of the free end of the jejunum (C'). When these sutures are tied, they intussuscept the previously inverted circular fold of the bowel wall toward the side where the short bite was taken; namely, toward the anastomosis.

Before closing the abdomen, a soft catheter may be introduced through the jejunal stoma for several inches beyond the gastrojejunostomy in order to facilitate early postoperative feeding.

To prevent the animal from pulling out the catheter, the latter should be anchored with a loose transfixing suture to the surrounding skin of the jejunal orifice.

Approximately 10 days after the operation, any suitable size or type of endoscope can be introduced through the jejunal stoma and valve for the inspection of the interior of the bowel. First air, then water, was used to distend the gut in order to make the examinations possible. This was not satisfactory because both air and water tend to escape from the site of the inspection, and permit the intestine to collapse over the instrument. Also, in the presence of ulceration,

a premature perforation of the gut may occur if the intraluminal pressure is not controlled.

At present, we are using a small, very thin, transparent rubber balloon tied over the tip of an ordinary cystoscope (Fig. 2). By means of a small bulb, it is

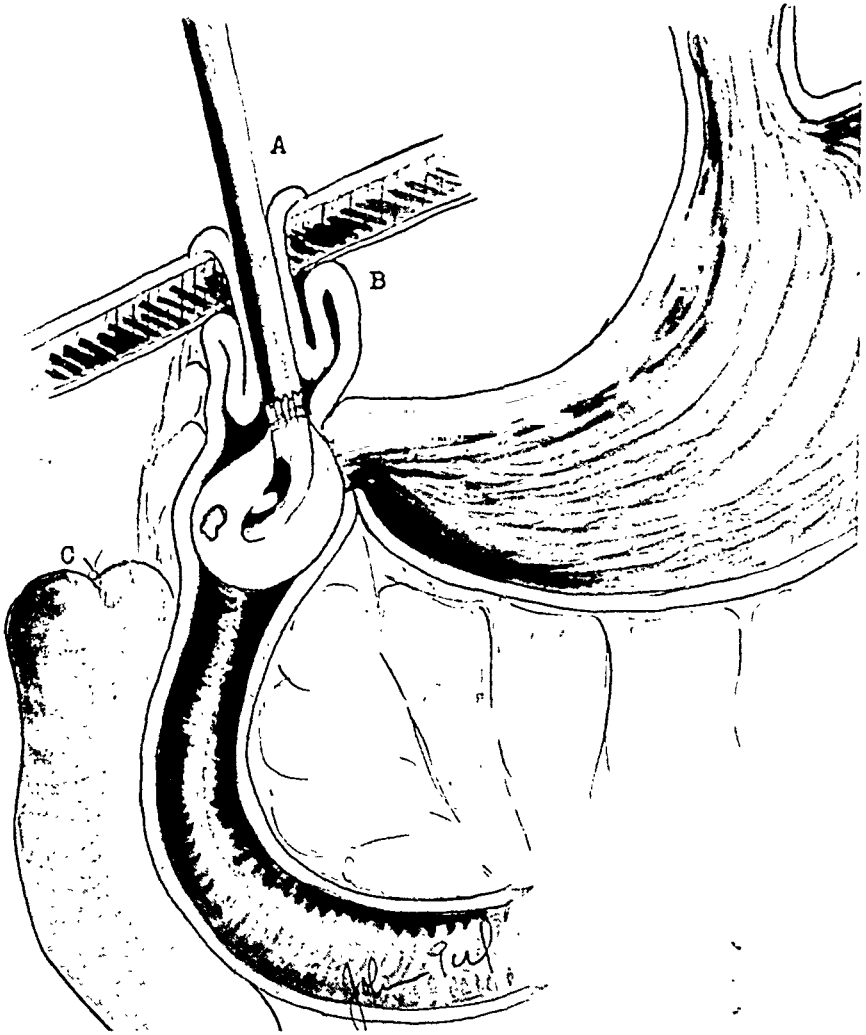


FIG. 2. Diagrammatic illustration of the operation with cystoscope introduced through the jejuna stoma and valve. Rubber balloon tied over tip of cystoscope is inflated with measured amount of air to facilitate inspection.

A: Jejunal stoma on abdominal wall.

B: Intussuscepted valve in jejunal stump.

C: Closed duodenal stump.

inflated with a measured amount of air to approximately 1 inch in diameter. Such a balloon will smooth out the mucosal folds of the bowel, and if the animal is not fed from the night before the examination, the field of inspection will be clear.

By intermittently inflating and deflating the balloon, the instrument may be manipulated to and fro within the lumen of the jejunum. One may also enter the stomach through the gastrojejunostomy and make a limited retrograde gastroscopy.

If the animal is restless, it is advisable to employ a short anesthesia for the duration of the inspection.

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THE ANTIGENIC PROPERTIES OF AN ENTEROGASTRONE PREPARATION*

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INTRODUCTION

It is imperative that any substance of animal origin which has characteristics of protein or protein derivative and is to be administered to human subjects by injection be tested for antigenicity before it is distributed for general use. This precaution is even more urgent if the substance must be administered repeatedly over long periods of time, since it is known that antigens of low potency can be made to demonstrate their antigenic capacity by repeated injection¹. The antigenicity of a therapeutic substance may be of importance for two reasons. First, because the sensitization of the patient is in itself harmful and unpleasant. Second, because the effect of the substance may be completely vitiated by the development of antibodies if the active principle is antigenic.

Enterogastrone, an extract of hogs' intestine, has been and is being tried for the treatment of peptic ulcer in man. The substance responds to several of the tests for protein and is administered repeatedly by injection. As far as we have been able to ascertain only one attempt has been made to investigate its antigenicity², and this with negative results. It seemed reasonable and desirable, therefore, to investigate further the antigenic capacity of the substance, employing more rigorous methods.

MATERIALS AND METHODS

The material tested consisted of two lots of a commercial preparation of enterogastrone³. It was prepared for use as directed, except that sterile triple distilled water was used instead of the diluting fluid provided because the latter contained a preservative. Solutions were freshly made immediately before use. The pH of this preparation was approximately 3.

Swine serum was obtained in the lyophilized form[†] and prepared in appropriate concentrations for use in sensitizing and eliciting the anaphylactic response.

One or two doses of a commercial horse serum preparation[‡] diluted 1:20 was injected in the early experiments to use as a positive control in the *in vitro* anaphylactic tests.

Young virgin female guinea pigs weighing between 190 and 400 grams at

* This study was aided in part by a grant from the Upjohn Co., Kalamazoo, Michigan.

† Kindly supplied by Armour and Co., Chicago, Illinois.

‡ Lederle Co.

the onset of the experiments were employed as the test subjects. Both *in vivo* and *in vitro* methods were adopted to demonstrate sensitization. The *in vitro* method made use of ileal strips according to the procedure of Nicholl and Campbell⁴.

Exposure of animals to the enterogastrone preparation was as follows: Injected quantities equivalent to 20 or 40 mgm. of the dry material were administered. A single course consisted of 1 to 3 intraperitoneal injections on successive days followed by a rest between courses of from 1 to 4 weeks. Following the final injection of any given series three weeks were allowed to elapse prior to attempting to elicit anaphylactic phenomena.

The distilled water solution of the enterogastrone preparation was found to have a primary toxic effect when administered intravenously to guinea pigs.

TABLE 1

ADMINISTERED SUBSTANCE	DOSE PER INJECTION MGm.	NUMBER OF INJECTIONS	TOTAL DOSE MGm.	NUMBER OF ANIMALS	NO. DYING IN ANAPHYLACTIC SHOCK*	NO. REACTING WITH IN VITRO ANAPHYLAXIS*
Experiment A						
Enterogastrone Preparation...	40	2	80	2	0/2	—
Enterogastrone Preparation...	40	7	280	4	3/3	1/1
Enterogastrone Preparation...	40	8	320	4	3/3	0/1
None.....	—	—	—	9	0/7	0/2
Experiment B						
Enterogastrone Preparation...	40 or 20	10	320	16	8/16	2/6†
Swine Serum.....	10	2	20	6	1/6	—
None.....	—	—	—	6	0/6	0/2†

* These are given as ratios of number of animals responding to number exposed to the enterogastrone preparation.

† Animals which survived *in vivo* test retested *in vitro* 3 weeks after the initial test.

This effect could be largely eliminated by neutralizing the material to pH 7.4 with solid sodium bicarbonate and followed by removal of the precipitate by centrifugation. The clear straw colored supernatant fluid was then administered via jugular vein in doses of 0.05 ml per 100 grams of body weight.

For *in vitro* tests the original solution of the preparation was dialysed overnight in the cold against 100 volumes of Ringer's solution, the precipitate removed by centrifugation and enough fresh Ringer's solution added to the dialysate to make a final dilution of 1:10. Even with this treatment a small atypical response could be elicited with some intestinal strips.

RESULTS

The results in the individual groups of the two principle experiments are summarized in Table 1.

A total of 80 animals were used in these experiments. Of these 33 died and are not included in the results. Most deaths were due to an intercurrent epidemic of diarrhea and a few to trauma incident to repeated intraperitoneal injection. Of the 47 remaining animals 15 were uninjected controls, 26 received the enterogastrone preparation alone or in combination with horse serum and 6 received porcine serum. None of the control animals produced either an *in vivo* or *in vitro* anaphylactic response. Fourteen of the 26 animals exposed to the enterogastrone preparation gave *in vivo* responses with typical death and 3 gave *in vitro* responses, or in all 65 per cent gave an anaphylactic response. One of the six animals sensitized with pig serum died in anaphylaxis when exposed to the enterogastrone preparation. In experiment B half of the animals receiving enterogastrone also received horse serum. No significant alteration in anaphylactic response could be attributed to the presence of the horse serum.

COMMENT

These experiments demonstrate that the enterogastrone preparation tested is antigenic, provided that a sufficient quantity of the material is administered. Thus, an anaphylactic response was elicited by *in vivo* or *in vitro* methods in seventeen of twenty-six animals receiving a total dose of 280 mgm. or more of the dried material. The low order of magnitude of the antigenicity of the material is brought out by relatively large quantities needed for sensitization compared with the small quantities of potent antigens such as horse serum, or egg albumin which are necessary to elicit anaphylactic phenomena in guinea pigs^{5, 6}.

That fact that one animal of six which had received swine serum as the immunizing agent died in anaphylactic shock following the administration of enterogastrone suggests that there may be some common antigenic factor in these two materials.

Since enterogastrone is capable of producing anaphylactic sensitization in experimental animals it should be used with caution in human beings. We may expect to find a certain percentage of persons exhibiting local or general reactions after prolonged treatment with enterogastrone. Whether or not certain persons sensitive to pork or pork products will exhibit sensitivity to enterogastrone without previous exposure to this material remains to be seen.

SUMMARY

A series of experiments designed to test the antigenic properties of enterogastrone were performed. Guinea pigs were used as the test subject. They were immunized with repeated intraperitoneal injections. *In vivo* and *invitro* tests of anaphylaxis were made. Seventeen of twenty-six guinea pigs injected with 280 mgm. or more of the dry enterogastrone gave characteristic anaphylactic

responses with one or the other of the two methods. One of six animals receiving swine serum as the immunizing agent gave an anaphylactic response when enterogastrone was administered intravenously. These experiments demonstrate that enterogastrone is an antigenic substance, though of a low antigenic potency. It is further suggested that enterogastrone and swine serum proteins are weakly cross antigenic. In view of these results, enterogastrone should be used with caution in man.

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FAILURE OF AN ENTEROGASTRONE PREPARATION TO INHIBIT GASTRIC SECRETION AND PREVENT RUMENAL ULCERS IN THE RAT*

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Considerable interest has been manifested in the possible treatment of peptic ulcer with enterogastrone. Experimentally, Ivy and his associates¹⁻³ observed inhibition of gastric secretion in dogs with gastric pouches and healing or prevention of stomal ulcers in animals prepared by the Mann-Williamson operation following the administration of enterogastrone. Results in pylorus-ligated rats, on the other hand, have been contradictory^{4, 5, 6, 7, 8}. In man, the effect of enterogastrone on the nocturnal and 24-hour gastric secretion has been erratic and transitory^{9, 10}; histamine- or insulin-stimulated secretion was not demonstrably reduced¹¹. Clinically, Greengard et al.¹² reported encouraging results in the prevention of recurrences in patients with peptic ulcer treated with an enterogastrone concentrate. Sandweiss¹³, however, did not observe this effect. In view of the varying experimental and clinical findings, it appeared desirable to investigate further the effects of an enterogastrone concentrate on gastric secretion and on the prevention of rumenal ulcers in the rat.

MATERIALS AND METHODS

The enterogastrone administered in these experiments consisted of two lots of a commercial product prepared from hog's intestine.[†]

White male rats (Sprague-Dawley), with body weights originally ranging between 128 and 165 grams, were fasted for 48 hours before ligation of the pylorus. The procedure followed was that of Shay et al.¹⁴ as modified by Pauls, Wick, and Mackay¹⁵. Operation was performed under ether anesthesia. The duration of experiments was 7, 8 or 9 hours.

Measurements were made of the volume and pH of the gastric secretion; the degree of ulceration in the gastric rumen was estimated according to the "ulceration index" of Pauls, Wick, and Mackay. In two experiments the free acidity was determined by the usual titration technique; in one study the total peptic activity was measured by the method of LeVeen¹⁶. The pH was estimated by commercial indicator papers,[‡] affording accuracy to approximately 0.3 units of pH.

The influence of several factors was examined. First, the dose of enterogas-

* This study was supported in part by a grant from the Upjohn Company, Kalamazoo, Michigan.

† Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

‡ pHydrion paper.

trone was varied from 5 to 100 milligrams per rat, equivalent to from 33 to 670 mg./kg. of body weight respectively. Second, the route of administration was altered, both intravenous and intramuscular routes being employed. In addition, multiple doses at 3-hour intervals were administered on the assumption that the effect of the concentrate might be transitory. Finally, the in-

TABLE I
Effect of Enterogastrone Upon Gastric Secretion and Ulceration in the Pylorus-Ligated Rat

EXPERIMENT NO.	NO. ANIMALS	ORIGINAL WT. (gm)	TREATMENT ENTEROGASTRONE	GASTRIC JUICE				INDEX OF ULCERATION
				Vol. (ml.)	pH	Free Acid (units)	Peptic Activity (units)	
I	7	151	5 or 10 mgm. I.M. at operation	6.4	2.6			2.3
	7	150	0	5.0	3.2			3.1
II	6	159	50 mgm. I.M. at operation	9.7	1.3*			2.7
	6	159	100 mgm. I.M. at operation	10.0	1.7			1.3
	6	158	0	10.6	1.7			2.5
III	9	141	3 doses I.V. 5 mgm. ea.	8.7	1.2	94	129†	0.1
	9	141	Saline I.V. 3 doses	8.7	1.6	71	155	0.2
IV	7	146	3 doses I.V. 5 mgm. ea. No additional ether anesthesia	5.1	2.2	44		1.2
	7	147	3 doses saline I.V. No additional ether anesthesia	5.9	2.1	62		1.4
	7	148	3 doses saline I.V. 2 additional ether anesthesia	4.7	1.9	59		1.7
Enterogastrone treated	Total	Av.		Av.	Av.	Av.	Av.	Av.
	35	149		7.5	1.9	69	129	1.4
No enterogastrone	36	149		7.4	2.1	69	155	1.8

* Determinations on 4 animals only.

† Average of determinations on 8 animals.

fluence of multiple short ether anesthetics on the degree of ulceration was investigated.

RESULTS

The results of the four experiments are averaged in Table I. Quantities of 5, 10, 50, and 100 mg. of the enterogastrone preparation, administered intra-

muscularly immediately following operation, had no apparent effect on the volume and pH of gastric secretion or the degree of ulceration (experiments I & II). In experiment III three doses each of 5 mg., administered intravenously at 3-hour intervals, likewise had no significant effect upon the volume, pH, free acidity, or peptic activity of the gastric juice. Only one of the treated animals and two of the control group manifested even slight ulceration, despite a 9-hour interval between ligation and sacrifice. The only significant deviation from the previous experiments with respect to the control group consisted of two additional ether anesthetics administered at the time of intravenous injection. The purpose of experiment IV was to determine, therefore, the possible role of the anesthesia in the prevention of ulcer; this study essentially constituted a repetition of experiment III except that injections in the treated group and in one control group were made without anesthesia. To a second control group two additional ether anesthetics were administered at 3-hour intervals. The results again demonstrate no influence of enterogastrone upon any of the measured components of gastric secretion or the degree of ulceration. Ether anesthesia did not reduce or prevent the formation of the rumenal ulcers, for "the index of ulceration" was even higher in the ether-treated group than in the other series. The grand averages for all treated animals and all control animals are recorded at the bottom of Table I. Ulceration was observed in 22 of the 35 treated animals as compared with 24 of the 36 control animals, an insignificant difference.

DISCUSSION

Previous studies of the effect of enterogastrone concentrates upon the gastric secretion and incidence of rumenal ulcers in pylorus-ligated rats have yielded variable results. Morris, Grossman, and Ivy⁴ failed to prevent ulceration in 46 of 47 rats receiving 25 to 500 mg. of the concentrate per kg. of body weight intramuscularly for 1 to 30 days prior to ligation. Administration of the preparation by intraperitoneal and intravenous routes likewise was ineffective. The volume of the gastric content averaged 6.5 cc. in the animals receiving the largest doses and 12.1 cc. in the control group. On the other hand, Visscher and Rayman⁵ reported inhibition of the 2-hour gastric secretion by 50 per cent, following the administration of 15 mg./kg. A comparison of the activity of enterogastrone with that of two anthelones prepared from human urine by Wick et al.⁶ indicated relatively little "antiulcer activity" of the enterogastrone preparation. Risley, Raymond, and Barnes⁷ observed an appreciable decrease in the degree of gastric ulceration following the intraperitoneal administration of 50 to 200 mg. of lyophilized dilute hydrochloric acid extracts of the upper 6 feet of the small intestine of hogs and of 50 to 100 mg. of enterogastrone prepared by the picric acid method. However, the results were variable and not all preparations manifested "activity". The oral administration of these ex-

tracts prior to ligation of the pylorus had no demonstrable effect. In general, the depression of gastric secretion paralleled the decrease in ulceration. However, the concentration of pepsin was elevated. Katz et al.⁸ noted an inhibitory effect on 6-hour gastric secretion following the intraperitoneal injection of 1 cc. of extracts prepared from lyophilized defatted duodenal mucosa of hogs.

The present experiments demonstrate no effect of the preparation of enterogastrone used upon the volume, pH free acidity, or peptic activity of the gastric secretion of rats. Similarly, there was no significant decrease either in the percentage of animals with demonstrable ulcers or in the degree of ulceration, despite the administration of quantities as large as 670 mg./kg. of body weight.

The possibility exists that the two lots of enterogastrone were inactive. However, this material was prepared in the same laboratory as was the concentrate used by Visscher and Rayman, who report significant effects. These investigators employed a somewhat different method, including cyclopal anesthesia and a 2-hour period of collection following ligation. Since their findings suggested that the action of the concentrate might be transitory, multiple doses at short intervals (3 hours) were administered in experiments III and IV, but with negative results.

The question may be raised as to whether the mechanism of gastric secretion in the rat differs from that in man or in dogs. Friedman¹⁷, in a well controlled series of experiments, demonstrated that in the pylorus-ligated rat histamine in doses up to 5.5 mg./kg. of body weight did not significantly increase the volume of gastric secretion and increased only slightly, if at all, the concentration of hydrochloric acid. This was in contrast to other species of animals including elasmobranch fishes, reptiles, and mammals. On the other hand, Harkins¹⁸ and his co-workers demonstrated that vagotomy could reduce the volume of secretion, the free hydrochloric acid, and the number of animals developing ulcers, even as in man. The apparent species difference may lie, not in the incapacity of the stomach of the rat to respond to histamine, but rather in the greater capacity of the rat to destroy histamine. Because of the potential usefulness of the rat for experimental investigation in the field of gastric physiology, this point perhaps merits further investigation.

There is a further possibility; namely, that the effect of enterogastrone is not manifested acutely in relation to its effect upon gastric secretion. Thus, it has been claimed that this substance confers upon the gastric mucosa an "immunity" to ulceration. However, the results of Morris, Grossman, and Ivy, previously described, do not demonstrate such an effect in the pylorus-ligated rat.

SUMMARY AND CONCLUSIONS

Enterogastrone was administered to groups of pylorus-ligated rats in single and divided doses, varying from 33 to 670 mg./kg. of body weight via both

intramuscular and intravenous routes. Comparison of a total of 35 treated animals with 36 controls revealed no significant differences in the gross percentage of ulceration, the degree of ulceration, or in the mean volume and pH of the gastric secretion. Sixteen treated rats showed no change in the free acidity when compared with 23 controls. Peptic activity in the gastric fluid of 8 animals did not deviate significantly from their 9 controls. Thus, enterogastrone did not appear to have an inhibitory influence upon the gastric secretion nor upon the tendency to ulceration in the pylorus-ligated rat under the conditions of these experiments.

Accumulated evidence from the literature suggests that there may be a gastric secretory depressant substance in extracts of the small intestine of hogs. To date, however, preparations of this type have had inconstant and frequently insignificant activity. It is apparent that, before such preparations can possibly be applied to the treatment of peptic ulcer, they must have a much greater potency and more constant activity.

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THE INTERPRETATION OF HISTAMINE AND INSULIN TESTS OF GASTRIC FUNCTION

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The physiological interpretation of histamine and insulin tests of gastric function has become a matter of practical import since Winkelstein & Hess¹ concluded from the results of insulin tests that the vagal nucleus is hyper-irritable in patients with duodenal ulcers. Further, they suggested that therapy should be directed towards reducing the vagal irritability with such potentially noxious methods as shock therapy. Their conclusion therefore deserves careful examination against modern concepts of the regulation of the acidity of the gastric juice. This paper attempts to show that their findings can be equally well explained on the basis of hyperreactivity of the peripheral secretory mechanism. Until this possibility has been excluded any drastic therapeutic attack on the central nervous system should be withheld.

Following the work of Hollander², and Gray & Bucher³ it is now widely believed that the gastric juice may be conveniently considered as a mixture of two components of constant composition; the acid parietal fluid and the remainder, or non-parietal fluid, containing ions of alkali metals, chloride ions and bicarbonate ions. At low rates of secretion the proportion of non-parietal fluid in the mixture is relatively high and the concentration of acid in the mixed juice is low since the parietal fluid is diluted and neutralised by the non-parietal fluid. Any increase in the rate of secretion is thought to be mainly the result of an increase in the rate of formation of the acid parietal component whilst the proportion of non-parietal fluid correspondingly falls. The concentration of acid in the mixture would then rise because the dilution and neutralisation by non-parietal fluid would become relatively less.

In their comparison of the gastric juice of patients with duodenal ulcers and normal subjects, Winkelstein & Hess used the highest concentration of acid observed in specimens collected for 15 minute intervals after the intravenous injection of insulin. It has been shown by Ihre⁴ that patients with duodenal ulcers secrete more rapidly than normal subjects under the stimulus of insulin. It is to be expected therefore that acid secreted at the highest rates of secretion in patients with duodenal ulcers would contain a smaller proportion of non-parietal fluid than the juice of normal subjects. The maximum acidity of the juice of patients with duodenal ulcer ought to be correspondingly higher than that of normal subjects. Winkelstein & Hess have shown this to be so.

This aspect of the chemical pathology of duodenal ulcer tends to be confusing since it has been shown by Ihre that the gastric juice of patients with duodenal

ulcer collected over one hour periods has a lower concentration of acid than that of normal subjects as may be seen from Table 1. Ihre's control group has a mean age 20 years lower than his patients. In order to assess the significance of this factor some results of Bloomfield & Keefer⁵ have been included. Their results lead one to expect a fall of about 11 m.eq./l. in the concentration of acid as a result of the 20 years difference in age between the normal subjects and the patients with duodenal ulcer. Since the difference recorded between normal subjects and patients with duodenal ulcer was 35 m.eq./l. it appears unlikely that age could account for the whole difference between the groups.

It is possible to account for Ihre's observations outlined above by assuming an increased basal secretion of non-parietal fluid in cases of duodenal ulcer. When the juice is collected over a whole hour period the proportion of non-parietal fluid to parietal fluid would be higher in patients with duodenal ulcer than in normal subjects in whom the concentration of acid would be correspondingly greater. When the juice is collected in fractions at short intervals

TABLE 1
Mean Concentration of Acid in the Gastric Juice
[Milli-equivalents/l (clinical units)]

	PATIENTS WITH		NORMAL SUBJECTS	
	Gastric Ulcer	Duodenal Ulcer	Ihre	Bloomfield and Keefer
Mean age.....	45	41	23	20 40
Mean conc. of acid.....	81.5	87.6	122.8	75 64
Standard error of mean.....	± 4.7	± 5.4	± 1.8	

the supranormal rate of secretion of acid component of the patients with duodenal ulcer would outweigh the effect of the raised secretion of non-parietal fluid in one or more fractions and thus lead to a supranormal concentration of acid. The assumption of an increased secretion of non-parietal fluid would be supported if patients with duodenal ulcer were found to secrete supranormal amounts of neutral chloride. From Ihre's figures it may be calculated that the normal subjects secreted a mean of 3.88 m.eq. (S.E. mean ± 0.27) of neutral chloride in response to histamine whilst patients with duodenal ulcer secreted a mean of 7.39 m.eq. (S.E. mean ± 0.43). These figures therefore are compatible with the assumption of an increased secretion of non-parietal fluid.

If the supranormal acidity of the juice of patients with duodenal ulcers is the sequela of the high rate of secretion rather than a specific response to insulin, any stimulus which raises the rate of secretion of patients with duodenal ulcer to higher levels than that of normal subjects would be expected to raise the acidity of the juice of patients with duodenal ulcers, collected at the height of its acidity, to values greater than those for normal subjects under the same

conditions. Pollard⁶ who stimulated secretion with histamine showed this to be so.

It may be concluded that part or even the whole of the difference between the patients with duodenal ulcers and normal subjects shown by Winkelstein & Hess may be the consequence of the raised rate of secretion. This does not dispose of the hypothesis that the vagal nucleus is hyperirritable, since the increased volume of secretion per hour of patients with duodenal ulcers may be its result. It becomes necessary to consider at this point the influence exerted by the vagal nucleus over the secretory functions of the gastric mucosa. Until recently it would have been acceptable to say simply that the psychic phase of gastric secretion was mediated by the vagus and that a discharge of impulses to the gastric mucosa could be produced by inducing a hypoglycemia. However it has now become apparent that the vagus may exert a form of trophic influence over the secretory mechanism since the response to histamine, which stimulates the mucosa directly, is reduced after vagotomy in patients with peptic ulcers. This aspect of vagal function must be passed over here but the better established secretory function will be examined.

The mechanism involved in the gastric secretory response to hypoglycemia must at its simplest contain three parts: receptors sensitive to hypoglycemia, the effector organ, the gastric secretory mucosa, and nervous pathways connecting the other two parts. Since no special receptors are known it is convenient to speak of the vagal nucleus as the part sensitive to hypoglycemia. Supranormal rate of secretion following a standard hypoglycemia might be due to hyperirritability of the vagal nucleus with a resulting supranormal discharge down the vagus nerves or to hyperreactivity of the gastric mucosa or to both factors acting together. An attempt is here made to determine where the abnormality lies.

It is well established that histamine stimulates the gastric secretory mechanism at the periphery. It seems possible that the reactivity of the stomach to histamine may be proportional to its reactivity to the normal nervous impulses coming down the vagus, although there is no proof of this hypothesis. If this assumption is granted it becomes possible to make comparisons of the reactivity of the stomachs of groups of individuals to normal nervous stimuli. For example if two groups respond equally to histamine, but unequally to insulin, the inequality may be said to lie in the central stimulatory mechanism. From the results of Ihre who tested groups of normal subjects and patients with peptic ulcers using both histamine and insulin, the mean figures for the amounts of Cl^- and pepsin secreted were computed. It may be seen from Tables 2 and 3 that patients with duodenal ulcer secreted 55% more Cl^- and pepsin in response to histamine than did normal subjects. Thus if the vagal centres of both groups were equally reactive one would expect that a standard hypo-

glycemia would result in 55% more chloride and pepsin from patients with duodenal ulcer than from normal subjects. Thus in order to eliminate the effect of variation in the secretory capacity of the mucosa from the total response to insulin, the response to insulin may be divided by the response to histamine. This has been done in the last columns of Tables 2 and 3. It may be seen that the values for $\frac{I}{H}$ are not significantly different from one another. Thus the whole of the hyperreaction to insulin can be accounted for on the basis of the hyper-reactivity of the gastric mucosa.

This does not exclude the possibility that the vagal nucleus is hyperirritable since there is no sure evidence that the response to hypoglycemia is not a maxi-

TABLE 2
Secretion of Cl⁻ in the Human Stomach after Stimulation with Histamine and Insulin

GROUP OF SUBJECTS	NO. OF SUBJECTS	MEAN SECRETION (Cl ⁻ /HR. MILLI-EQUIV.)		$\frac{I}{H}$
		After Histamine (H)	After Insulin (I)	
Normal.....	24	16.11(±1.25)	21.62(±1.54)	1.34(±0.14)
Duodenal Ulcers.....	19	24.81(±2.00)	27.92(±2.27)	1.12(±0.14)
Gastric Ulcers.....	20	14.75(±1.97)	20.19(±2.58)	1.37(±0.25)

Standard errors are shown in parentheses.

TABLE 3
Secretion of Pepsin in the Human Stomach after Stimulation with Histamine and Insulin

GROUP OF SUBJECTS	NO. OF SUBJECTS	MEAN SECRETION OF PEPSIN (UNITS/HR)		$\frac{I}{H}$
		After Histamine (H)	After Insulin (I)	
Normal.....	24	3453(±309)	7639(±730)	2.21(±0.29)
Duodenal Ulcers.....	19	5372(±401)	13096(±1460)	2.43(±0.40)
Gastric Ulcers.....	20	3372(±487)	8790(±1115)	2.61(±0.50)

mal secretory effort. If this were so, any supranormal reactivity of the vagal centre would not be followed by any corresponding increase in gastric secretion. There is indirect evidence that the response of the stomach in Ihre's experiments was not maximal. It seems probable that the mechanisms for the secretion of chloride and acid are indefatigable. Since the response to insulin was not uniform throughout the hour in Ihre's experiments, there would have been an opportunity of increasing the rate of secretion per hour if the highest rate of secretion had been maintained longer.

Thus it appears that the evidence available suggests that the hyperreactivity of the gastric mucosa is sufficient to account for the supranormal concentration of acid demonstrated by Winkelstein & Hess and the increased amounts of secretion found by Ihre in patients with duodenal ulcers.

The reduction in the secretory response to histamine following vagotomy suggests that the hyperreactivity of the gastric secretory mechanism could be related to some trophic action of the vagus nerves. The only clue to the nature of this influence is that in Ihre's patients with duodenal ulcers the secretory response to histamine was equally raised for pepsin and chloride. If this finding is more than a coincidence its interpretation is very difficult according to current hypotheses of gastric secretory regulation. The only factor common to the secretion of pepsin and chloride would appear to be vascular supply.

It should be clear from what has been said above that the general interpretation of the histamine and insulin tests of gastric function still rests on most unsure foundations. It therefore seems premature to attempt any potentially harmful attack on the central stimulating mechanism with the object of reducing the hypersecretion in response to insulin of patients with duodenal ulcers.

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Case Reports

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VAGOTOMY AS A CURE FOR THE POST-GASTRECTOMY DUMPING SYNDROME

A CASE REPORT

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The occurrence of the so-called "dumping-syndrome" poses a therapeutic problem in the after-care of gastrectomized patients. In the first few post-operative days the naturally limited diet is well tolerated. But as the diet progresses to liberal amounts, the syndrome is liable to supervene. This picture is characterized by epigastric heaviness and distention, flushing, profuse perspiration, nausea, weakness, uneasiness, headache even to the point of vomiting, fainting and nervousness. The symptoms are exaggerated by walking immediately after meals, relieved by rest, and by the reclining position. The symptoms may persist for years. The occurrence of this "small-stomach" syndrome or "explosion-evacuation syndrome" varies according to the quoted statistics, usually between 3 and 5 per cent; according to Custer, Butt and Waugh¹ it was as high as 12 per cent; Bruusgaard found it present in even 15 per cent of gastrectomized patients.

For a time the syndrome was ascribed to a hypoglycemia resulting from immediate and rapid absorption of monosaccharides, exaggerated pancreatic response and a reactional hypoglycemia. Glaessner, on the contrary, attributed the symptoms to an early hyperglycemia resulting from too rapid an absorption of simple carbohydrate in solution, and was convinced that he could reproduce the phenomena by the instillation into the jejunum of 300 cc. of a 50% solution of glucose. Subsequent observations on the part of many authors have not substantiated the theory either of hypoglycemia nor of hyperglycemia as a satisfactory explanation of the syndrome.

The mechanical explanation of the "dumping syndrome" seems to be far more convincing. The explosive evacuation from the stomach and the subsequent over-distention of the anastomotic loop with the resultant alteration of the physiological regulatory mechanism, possibly through abrupt splanchnic congestion, offers a more likely explanation of the mechanism. The hyperemia of the splanchnic area leads to cerebral anemia. The symptoms are likely to

persist until the small volume of the amputated stomach enlarges to contain a larger amount of food before the evacuating mechanism allows of emptying or dumping (six months to several years).

The attempt to avoid the syndrome has led to the concept of reducing the size of the anastomosis between the stump of the stomach and the jejunum by substituting the Hofmeister modification of the Polya operation or a Schumacher modification of the Billroth I procedure.

The best results seem to be obtained by dietary management, the leading concept of which is small meals, little bulk, avoidance of fluids with meals and postprandial rest. In my own studies on the "dumping syndrome" the best results have been obtained by dividing the diet into two-hourly feedings, the bulk of food being reduced to 200 to 300 grams per meal. The protein bulk must be concentrated, fats and carbohydrates relatively reduced. Carbohydrates other than monosaccharides may be liberally apportioned; fluids should be drunk between rather than with meals. Postprandial rest is essential. Medicinal treatments have been essayed such as dilute hydrochloric acid, ephedrine sulphate, doryl as a stimulator of smooth muscle in the alimentary tract, but with little or no satisfactory result.

A striking result, however, was seen in one case of severe "dumping syndrome" by the utilization of vagotomy to overcome the syndrome. The patient, a man 46 years of age, had undergone a subtotal gastrectomy in September 1946 for duodenal ulcer. Within a few weeks the postprandial distress was so severe that even the drinking of a glass of water would produce epigastric distention and distress, perspiration, weakness, almost to the point of fainting. The post-prandial blood sugar was 90 mgm. per cent at the moment of greatest intensity of symptoms. Under fluoroscopy, the distal loop of jejunum filled very rapidly, was quickly distended and emptied with equal acceleration.

Unable to control the symptoms by any medical or conservative means, a trans-thoracic bilateral vagotomy was performed (Dr. J. C. B. Molbran) in the hopes of attaining a moderate degree of gastric atony and dilatation such as is commonly seen to occur after primary vagotomy. Within twenty hours after operation, limited fluids were tolerated by the patient without discomfort. The size and character of the meals were enlarged by the addition of concentrated solids until 500 grams per meal were instituted without distress on the part of the patient. One year later the patient has gained fifteen pounds, eats a full meal without the slightest distress and is restored to natural physical efficiency.

The radiographic study made several months after the vagotomy showed a distention of the gastric stump to twice its former size, a definite reduction in peristaltic activity, relatively delayed evacuation and lessened dilatation of the

efferent loop of the jejunal anastomosis. While it may not be logical to attribute to the vagus nerves the causation of the hyperirritability of the post-operative gastric stump, it certainly seems clear that the section of the pneumogastric nerves ameliorated or eliminated the dumping syndrome with relief, in this one case at least, of all subjective symptoms.

It is hoped that this case report will stimulate others to attempt to utilize vagotomy for the control of the very embarrassing and distressful symptoms associated with the postoperative "dumping-syndrome."

CICATRIZING ENTERITIS, COLITIS AND GASTRITIS

A CASE REPORT

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Prior to 1932 there had been little organized or well integrated knowledge of the entity which, since that time, we have come to recognize commonly as regional or cicatrizing enteritis. It was then that Crohn, Ginzburg and Oppenheimer¹ initiated a new cycle of interest in this disease by their analysis and classification of a series of cases fitting appropriately into a newly termed but long irregularly recognized syndrome. Since then the recognition of this disease has progressed rapidly as is evidenced by the ever increasing analyses and case reports which have appeared designating many points of interest in this disease. Much has been recorded regarding the segmental occurrence of cicatrizing enteritis, its "skip" areas and "string" signs, its complications requiring surgery, the probably fundamental defect in lymphatic drainage, and the great tendency for recurrence and contiguous extension of this disorder after surgery. The purpose of this paper is to submit data on a case of cicatrizing enteritis which epitomizes some of the characteristics commonly recognized in this disease. Information concerning the appearance of a gastric lesion during the course of this patient's illness suggesting its intimate relationship to her pre-existing cicatrizing disease is presented.

REPORT OF A CASE

First Admission. August 23, 1946, weight 120 pounds; discharged September 3, 1946, weight 111 pounds.

This 21-year-old single white woman had enjoyed good health until January 1944 when for the first time right lower quadrant, cramp-like abdominal pain of intermittent character occurred and was associated with diarrhea consisting of four to five loose nonbloody dejections daily. Because of progression of her symptoms she entered another hospital where an appendectomy was performed in April 1945 and the diagnosis of regional ileitis was made. In April and June of 1945, following appendectomy, rectal abscesses developed and were drained surgically. Her immediate postoperative course was uneventful but symptoms gradually returned after several weeks. Abdominal pain appeared early and persisted. Diarrhea began approximately six weeks prior to this admission. The patient developed anorexia and had lost 16 pounds the preceding twelve months. During the spring of 1946 she received two roentgen treatments to an area of keloid formation, without improvement. Low back pain of mild degree was present. The menstrual history was normal although the above pains were augmented by the menses.

Physical Examination. The blood pressure was 112 mm. systolic and 74 mm. diastolic, pulse 84, regular rhythm. The patient was well developed and fairly well

nourished and except for a hard, tender mass in the right lower quadrant of the abdomen the examination was negative. Temperature, pulse and respirations remained normal.

Laboratory Data. Urinalysis was essentially normal. Blood picture was as follows: hemoglobin 10.2 gm., erythrocytes, 3,600,000, leukocytes, 14,000, polymorphonuclear cells, 70, band forms, 10, lymphocytes, 20, nonprotein nitrogen, 31 mg., total protein, 6.7 gm., serum bilirubin, 0.4 mg., sodium chloride, 536 mg. per 100 cc. and prothrombin time, 70 per cent. Feces were negative for occult blood.

Röntgen Data. Upper gastrointestinal examination was normal except for a "string" sign involving the terminal ileum, characteristic of regional ileitis. This was verified by barium enema. The colon was normal. Stereoscopic x-rays of the chest disclosed the lungs to be clear.

On August 29, 1946, laparotomy was performed at which time resection of the terminal ileum and right colon with primary anastomosis was accomplished. The terminal 18 to 20 cm. of ileum was markedly indurated, thickened and reddened. There were several adhesions between involved loops of intestine and pelvic viscera. The mesenteric nodes were enlarged. Histopathologic examination was typical of cicatrizing enteritis with slight hyperplasia of lymph nodes.

Postoperative Course. There was the usual mild fluctuation of temperature, pulse and respirations to levels of 103°, 125 and 15 respectively following operation. Gradual return to normal values occurred at the end of the fourth postoperative day.

The postoperative convalescence was assisted by administration of three transfusions, parenteral penicillin, sulfadiazine, fluid and electrolytes. At the time of discharge on the fifteenth postoperative day she was having one soft-formed defecation daily. Her diet was bland, without fruits and supplemented with multivitamins.

Second Admission. November 3, 1947, weight 122 pounds; discharged December 20, 1947, weight 102½ pounds.

The patient's condition was good for one year. Her appetite, activity, and weight had returned to their preoperative normal levels. A telegram was received in October 1947, however, stating that she had recurrent abdominal cramps of diffuse character, nausea, no emesis and frequent loose, nonpurulent and nonbloody stools.

On admission there had been obvious anorexia with resultant 11 pound weight loss occurring over a period of three months, flatulence, hyperperistalsis, eructation, abdominal soreness and generalized abdominal tenderness. The descending colon was palpable.

On November 12, a minimal dose (5,000,000 organisms) of typhoid vaccine was administered but the desired febrile level was exceeded, temperature rising to 104.5°, and it was, therefore, deemed inadvisable to continue this approach to the problem. The temperature then fluctuated between 98.6° and 102.5° until surgical intervention on November 26.

Digital rectal examination was negative; proctoscopy to a level of 7 inches revealed a shiny, edematous, friable mucous membrane which bled easily where wiped with cotton. The diagnosis was ulcerative colitis.

On November 22, a large fissure which is a not uncommon and bad complication of ulcerative colitis appeared on the posterior anal wall. This was treated with wet dressings, liberal applications of vaseline, and opium suppositories.

Laboratory Data. Urine was normal. Blood picture was as follows: erythrocytes 3,970,000, leukocytes, 6,500, hemoglobin, 12.6 gm., polymorphonuclear cells, 47, band forms, 10, lymphocytes, 27, eosinophils, 7, basal sedimentation rate, 73 mm., prothrombin time, 72 per cent; total protein, 7.2 gm., albumin, 4.4 gm., globulin, 2.8 gm., sodium chloride, 528 mg., gastric analysis, mucus 1 plus, volume, 15 cc., food content, 5 per cent, free hydrochloride, 57 degrees, total acid, 85 degrees, occult blood, 0. Feces, 0 to 3 plus for occult blood. Six specimens for culture were negative for enteric pathogens; three negative for ameba and ova of parasites.

Roentgen Data. The upper gastrointestinal series again revealed a normal esophagus, stomach and duodenum. There was slightly delayed emptying of the stomach. A questionable area of involvement of the mid ileum appeared proximal to the anastomosis. The colon was normal but slightly spastic. Visceral outlines were normal. There were no unusual gas shadows.

Because of subjective and objective evidence of recurrent intractable disease the patient was again submitted to surgery on November 26. Cicatrizing enteritis involved the area of the anastomosis and extended proximally for a distance of 6 inches. The involved tissues and mesenteric nodes were greatly thickened. The colon was only slightly edematous from here to the rectosigmoid junction.

Surgical Diagnosis. Recurrent ileitis with chronic ulcerative colitis.

Operation. Divided ileostomy.

Postoperative Course. The immediate postsurgical course was smooth with the routine gradual decline of the fever which had reached a level of 103° on the day of operation. Normal levels were reached and maintained from the fifth postoperative day until discharge. Three blood transfusions, amigen, parenteral penicillin and vitamins supplemented the usual postsurgical electrolyte and fluid replacement therapy. Trouble was soon encountered, however, with impaired drainage through the ileostomy. This required insertion of a catheter which remained *in situ* at dismissal from the hospital. Similar dietary regulations were imposed as above indicated, together with supplementary antispasmodics.

Third Admission. December 25, 1947, weight 102 pounds; discharged March 22, 1948, weight 98½ pounds.

Five days had elapsed between these two admissions and it was a period of great misery and turmoil for the patient, characterized by recurring severe abdominal cramps, emesis and distention associated with nonfunctioning of the ileostomy. Irrigations together with parenteral fluid and electrolyte replacement were frequently employed in an attempt to restore normal drainage through the ileostomy, but surgery was eventually required.

Laboratory Data. The urine was normal. Blood picture was as follows: hemoglobin, 10.8 gm., erythrocytes, 4,590,000, leukocytes, 9,000 to 15,000, polymorphonuclear cells, 48, band forms, 21, lymphocytes, 27, monocytes, 2, abnormal lymphocytes, 2, sodium chloride, 446 mg. initially, later restored to normal values, blood calcium,

7.7 mg. per 100 cc., later 9.7 mg. per 100 cc., total protein, 6.7 gm., albumin, 3.6 gm., globulin, 3.1 gm.

Roentgen Data. After the second operation the stomach and duodenum were normal; no delay at the stoma, delayed emptying from the stomach, there being 50 per cent gastric residue at eight hours. The delayed emptying time was thought to be functional in origin, perhaps nutritional.

Electrocardiographic Findings. Reported normal with right axis deviation.

On January 10, 1948, a laparotomy was performed. The ileum was dilated and a kink in the intestine close to the abdominal wall proximal to the stoma was discovered. The transverse colon, sigmoid colon and rectum appeared thickened and edematous.

Diagnosis. Ulcerative colitis, partial obstruction in the functioning ileostomy due to a kink in the bowel.

Operation. Reconstruction of a new ileostomy; resection of the left transverse, descending and sigmoid colon.

Histopathology. Chronic ulcerative colitis with involvement of the ileum.

The initial postoperative course was satisfactory but thirty-eight days after the foregoing surgical procedure, due to recurrent malfunction of the ileostomy surgical revision of the stoma was again necessary. Exploration disclosed many adhesions between the coils of lower small intestine and abdominal wall. A stricture appeared at the level of the abdominal wall. The ileum was thickened and indurated.

Surgical Diagnosis. Ulcerative colitis; malfunctioning ileostomy.

Operation. Revision and new implantation of ileostomy.

Histopathology. Ulceration; subacute and chronic inflammation.

Her hospital convalescence following this latter operation was complicated early by hypochloremia, cramps and emesis, but these were gradually overcome by conservative management and the patient was discharged on the eighty-ninth hospital day. Twenty-five hundred cubic centimeters of blood, parenteral penicillin, vitamins, and fluid with electrolyte were freely used during this period. Dietary measures similar to those previously employed were again instituted. The patient's condition, chemically and clinically on discharge was entirely satisfactory.

Fourth Admission. August 18, 1948, weight 130 pounds; discharged September 3, 1948, weight 130 pounds.

The patient was admitted in fine physical condition for the purpose of performing the last stage of a colectomy. On August 20, a Miles abdominoperineal resection was carried out without incident. There were no intraperitoneal adhesions. The portion of large intestine removed was rather edematous.

Laboratory Data. Urine was normal. Blood picture was as follows: hemoglobin, 12.5 gm., erythrocytes, 4,790,000, leukocytes, 10,500, polymorphonuclear cells, 76, lymphocytes, 22, monocytes, 2, total protein, 7.2 gm., sodium chloride, 475 mg. to 512 mg. per 100 cc.

Surgical Diagnosis. Chronic ulcerative colitis.

Operation. Miles abdominoperineal resection.

Histopathology. Chronic ulcerative colitis, inactive phase.

The hospital progress during this admission was entirely uneventful and she was given a general hospital diet on the thirteenth postoperative day. The ileostomy was functioning satisfactorily.

Fifth Admission. February 13, 1949, weight 113½ pounds; discharged March 2, 1949, weight 110 pounds.

There had been no subjective complaints save for mild anorexia and obvious 17 pound weight loss since her last hospital admission. There were no upper gastrointestinal symptoms except that she had been experiencing upper abdominal pain for one month and recently had been running a mild fever. Beginning one week prior to this admission the patient for the first time noted a mass the size of a golf ball in the left rectus scar which initially was tender but this tenderness soon disappeared. The mass was thought to represent an abscess in the abdominal wall. The ileostomy was functioning exceptionally well.

Laboratory Data. The urine was normal. The blood picture was as follows: hemoglobin, 11.8 gm., erythrocytes, 4,390,000, basal sedimentation rate, 60, and sodium chloride, 561 mg.

On February 15, 1949, preparations were made for local incision and drainage of an abdominal wall abscess but this was abandoned when the mass proved to be intraperitoneal. A full scale abdominal exploration was undertaken by extending the primary incision. Examination of the intraperitoneal contents revealed a palpable mass involving the greater curvature of the stomach in its distal third. It was adherent to the pancreas posteriorly and extended into the pedicles of the middle colic vessels. The pancreatic tissue adjacent to the mass was indurated. The measurements of this lesion were approximately 3 by 3 by 3 inches. After detachment from the adherent structures a biopsy was taken and was reported on frozen section as chronic diffuse inflammation.

Operation. Partial gastrectomy (one half of the stomach resected); Billroth I; gastroduodenostomy.

Histopathology. Before microscopic examination approximately 8 cm. from the distal resected margin there was a diffusely hard, ovoid mass, measuring approximately 5.0 cm. in its greatest diameter. It was indistinguishable from the stomach wall. The remainder of the serosa was negative. On the mucosal aspect of this mass was a circular punched-out ulcer measuring 1.0 cm. in its greatest diameter. The mucosal surface surrounding the ulcer was inflamed and edematous but not overhanging or indurated. The base of the ulcer was diffusely grayish-red in color. The indurated mass extended equally in all directions from the base of the ulcer measuring about 2.5 cm. in thickness to the free margin of the adherent omentum. The remainder of the mucosal surface was negative except that the rugae were puckered toward the ulcer crater.

Microscopic Diagnosis. Phlegmonous gastritis with ulceration, probably extension of cicatrizing enteritis.

The postoperative course was entirely similar to that routinely witnessed after

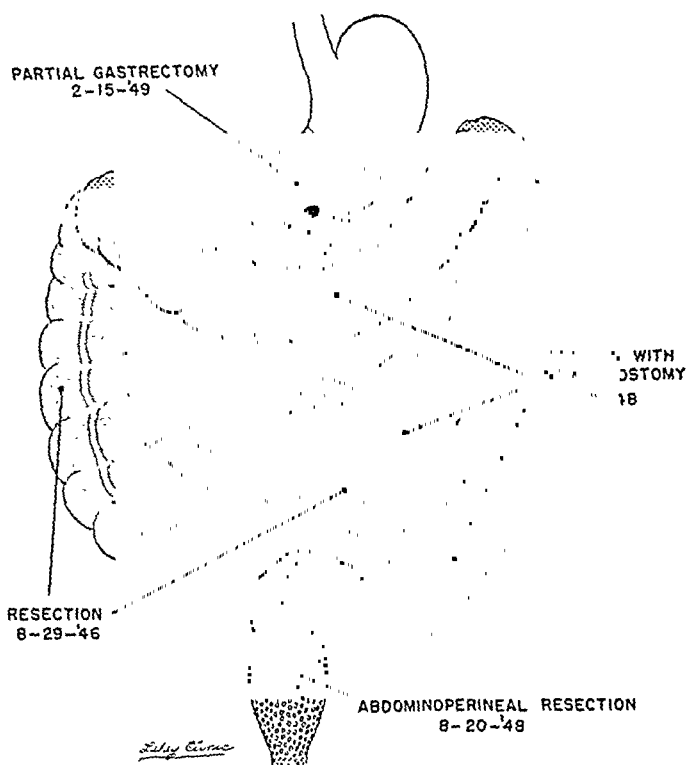


FIG. 1. August 29, 1946. The terminal 14 inches of ileum were involved in disease.

Operation. An hemicolectomy with primary anastomosis was performed involving removal of the terminal 20 inches of ileum together with the cecum and ascending colon.

November 26, 1947. The terminal 6-inch segment of ileum proximal to the anastomosis was involved in recurrent disease. Chronic ulcerative colitis to a minimal degree appeared for the first time extending from the area of the anastomosis to the splenic flexure. The descending sigmoid and rectal segments were grossly normal.

Operation. An ileostomy was accomplished with implantation of the terminal ileum as a nonfunctioning ileostomy.

January 10, 1948. Localized recurrent disease involving the terminal ileum 5 inches proximal to the stoma of the functioning ileostomy. The colitic process noted above appeared at this time to include the entire remaining colon and rectum.

Operation. Reconstruction of a new ileostomy with resection of 8 inches of terminal ileum including the area of localized recurrence, also removal of 10 inches of ileum measuring 10 inches, together with the remainder of the transverse colon.

February 17, 1948. A stricture developed in the ileostomy associated with thickening and induration of the adjacent small intestine. Adhesions between coils of small bowel and abdominal wall were apparent in the region of the ileostomy.

Operation consisted of diversion and reimplantation of the ileostomy.

August 20, 1948. There were no intraperitoneal adhesions. The rectum as previously noted was involved in disease.

Operation. A Miles abdominoperineal resection was performed.

February 15, 1949. Localized cicatrizing disease in which there was mucosal ulceration, involved the greater curvature of the stomach. When viewed grossly, the entire lesion measured approximately 3 inches in diameter. Involvement of contiguous pancreatic tissue and pedicles of the middle colic vessels in this process was also apparent.

Operation. Partial gastrectomy (one-half of stomach removed), Billroth I; gastroduodenostomy.

Note: 38 inches of terminal ileum were removed during these procedures.

partial gastrectomy and the patient was dismissed from the hospital on a dietary program containing meats and pureed vegetables given in five small feedings daily.

COMMENT

This report detailing a case of cicatrizing disease of the gastrointestinal tract has several points of interest. It is believed that the pathogenesis and histologic characteristics of the gastric lesion appearing here are identical with the cicatrizing process of the small intestine which this patient initially presented. If this presumption is accepted, it then localizes for the first time the proximal extent of the disease above the small intestine. The segmental nature of this entity and associated interference with lymph drainage frequently discussed are brought into focus. The question of extension of the disease to the stomach by contiguity in view of involvement of the adjacent transverse colon is raised. This cannot be categorically disproved and perhaps this is the mode of extension of the disease in this instance. The colon certainly was involved characteristically in this fashion. It is to be recalled, however, that in the more recent surgical history of this case the abdominal contents were strikingly free of adhesions. Also, at no time was there evidence of disease involving the intervening small intestine proximal to the initial lesion in the terminal ileum. These factors mitigate to some extent at least against the theory of contiguous extension to the stomach. On the other hand, the gastric lesion occurring along the greater curvature of the stomach is in one of the areas where lymph drainage for this organ is concentrated. The historical tendency for this disease to recur and extend is here poignantly demonstrated so that for the first time there seemingly has been encountered, in sequence, cicatrizing ulcerative enteritis, colitis and gastritis.

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CASE REPORT OF A NEUROFIBROMA OF THE JEJUNUM WITH INTUSSUSCEPTION

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Of the rare non-malignant neoplasms of the small intestine, the neurofibroma is seen least frequently. It may occur as a manifestation of a generalized neurofibromatosis, first described by von Recklinghausen in 1882, or as an isolated tumor.

Visceral neurofibromas may occur as solitary or multiple growths. They may develop at any site in the gastrointestinal tract. They are essentially benign but may undergo sarcomatous change.

The histogenesis of tumors associated with peripheral nerves has evoked much discussion and confusion. Two schools of thought are still extant; according to the one, these tumors arise from the endo and perineural connective tissue; while the other places the site in the cells of Schwann. Penfield¹ excellently summarizes tumors of the sheaths of the nervous system and adheres to the connective tissue hypothesis. The Schwannian theory is defended by Masson². An excellent review is given by Foot³.

Collins⁴ reviewed 18 cases operated on since 1929, all but one being of the solitary type. 12 of these were benign and 6 malignant. One additional case is reported and described by him. Lindenmeyer⁵ presented a case of multiple neurofibromas of the intestinal tract. He stresses its origin from the myenteric plexus of Auerbach, and divides neurofibromas into the following groups; 1) Intestinal neurofibromas as an accompaniment of generalized neurofibromatosis, 2) Intestinal neurofibromas as an isolated phenomenon, 3) Intestinal neurofibromas with sarcomatous change, 4) Intestinal neurofibromatosis with massive local tumor formation.

Baker and Halley⁶ report two neurofibromas of the small intestine associated with massive hemorrhage. One occurred 17 inches from the ileocecal valve and the other 35 inches from the ileocecal valve.

Hudlung⁷ reviewed 18 cases of neurinoma of the small intestine and described an additional case in a woman aged 60 with marked anemia and melena. At operation a non-obstructing tumor in the mid-portion of the ileum was removed.

A neurofibroma is essentially a fibrous type of neoplasm derived either from the sheath cells of Schwann, or from the fibroblasts of the delicate framework of connective tissue supporting the nerve fibers. There is a marked tendency to the production of fibrils of reticulum and sparse fibrils of collagen. They

form interlacing bundles of parallel fibers. These tumors may arise both from the perineurium or endoneurium (mesodermal) and also from proliferation of nerve sheath cells or cells of Schwann (ectodermal) ⁸.

The neoplasm may be subserous, intramuscular, intra or extraluminal, or it may be attached to the serosa and be pedunculated. It is firm, solid, and gray or dusky red. Intussusception may occur secondarily.

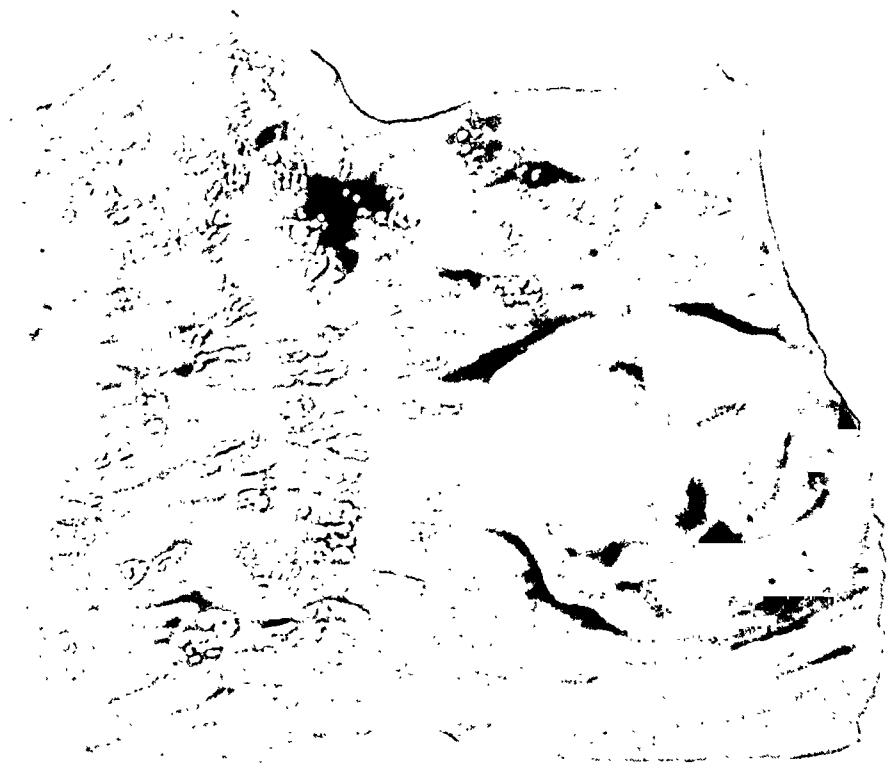


FIG. 1. Showing the mucosal surface of the ileum with the protruding tumor.

Intestinal neurofibromas may be symptomless or may produce vague intestinal discomfort. Most commonly the symptoms of intussusception lead to the discovery of the growth at operation. Slight prolonged or severe acute intestinal hemorrhage may occur, and suggest the diagnosis of small bowel tumor. Volvulus may occur in the pedunculated form.

The following case report is offered as a characteristic example of intestinal neurofibroma discovered at operation for bowel obstruction due to intussusception.

Clinical History (P.M.H. case #96499) This 38 year old white male, a school teacher by occupation, was admitted to Passavant Memorial Hospital on 4-8-47. In November 1946, the patient had an attack of severe sharp abdominal pain, sudden

in onset, which lasted all night and occurred intermittently during the next day. The pain was accompanied by continuous nausea and emesis. The following day a physician was consulted and a diagnosis of probable food poisoning was made. Since this episode, the patient experienced occasional similar slight intermittent attacks until two weeks prior to admission when he had another severe attack of vomiting and severe abdominal pain. After persisting all night, the patient was admitted to another hospital where a blood transfusion was given because of anemia. Intermittent



FIG. 2. Neurofibroma showing the relation of the nodule to the intact mucosa. H & E preparation $\times 90$.

attacks of pain persisted until 4-8-47 when the patient was transferred to Passavant Memorial Hospital following a severe attack of pain. During the episodes of pain, the patient has noted a hard "swollen" area just to the left and inferior to the umbilicus with relief from his pain when this disappeared. There is a history of weight loss of 20-30 pounds since the onset of symptoms.

In 1934 the patient underwent a gastroenterostomy, presumably for a duodenal ulcer. In 1935 he was reoperated and a degastroenterostomy and appendectomy was performed. Since this operation the patient has had repeated episodes of tarry stools and more recently of bright red blood in the stools. Because of the extent of the latter, he has been hospitalized on several occasions for transfusions.

The family history is non-contributory.

Physical Examination: The patient was highly nervous, coughing and retching. The B.P. was 158/92, temperature 99 (R), pulse 68. The abdomen was soft and flat except for an area extending from just below the umbilicus over the left rectus to a point about 15 cm. superior which was tender and offered some resistance to palpation. Auscultation of the abdomen was normal except over the above mentioned area where peristaltic sounds were almost continuous and markedly exaggerated. The rectal examination was negative. The remainder of the physical examination was negative.

Laboratory Urinalysis: pH, 5.5; Sp. Gr. 1.026; albumin and sugar negative; R. B. C. 4.00; Hgb. 11.1 gm.; W.B.C. 11,650; Sed. rate, 21; Kahn, negative. Urea nitrogen, 10.6; Blood calcium 11.4; Carbon dioxide combining capacity, 42.8%.

X-ray Examination: The scout film of the abdomen shows "considerable air in the stomach and in the colon, but a striking amount of air in a large jejunal loop which stretches more or less transversely across the abdomen, from a point 2 inches to the right of the spine to a point near the splenic flexure of the colon."

Umbrathor was administered and a two hour film showed a normal prepyloric region, pyloric canal and duodenal bulb. The third portion of the duodenum is wider than average. At 16 hours there is still a definite residue in the dilated loop of small bowel which could be identified as an upper jejunal loop.

A celiotomy was done 4-9-47, following decompression and hydration. A sausage-shaped intussusception was found which extended from the left upper quadrant across the abdomen to the right upper quadrant. When delivered into the incision it proved to be about 18 inches long and started approximately one foot distal to the duodeno-jejunal junction. After the intussusception was reduced, a firm tumor mass was seen within the lumen of the jejunum. The segment of bowel containing the tumor as well as the intussusception was resected and an end to end anastomosis effected.

The postoperative course was uneventful and the patient was discharged on the tenth postoperative day.

Pathologic Report: The specimen consists of 92 cm. of small intestine and the attached mesentery. Sixteen cm. from one end a firm nodular tumor mass is noted. It measures 4 x 3.8 x 3.8 cm., and on cut section consists of white, soft to firm tissue. Traversing this white tissue are interlacing strands of connective tissue. The serosal surface overlying this mass is smooth. The mucosal surface is ulcerated. The mass of the tumor protrudes into the lumen of the bowel. The remaining portion of the bowel is normal. No definite nodules are palpated in the mesentery.

Microscopic Description: Several sections through the tumor show essentially similar findings. The mass has raised the mucosa which is ulcerated and largely absent on the luminal aspect of the tumor mass. This denuded surface is hyperemic, edematous, with a superficial zone of fibrinoid necrosis and marked cellular infiltration of acute type. On the other surface, the tumor has replaced much of the muscularis. It consists of spindle-shaped cells which show a striking tendency toward

fasciculation and palisading. The cells are compactly arranged in some areas and more widely separated in others. The nuclei are elongated with both tapering and blunt ends observed; the nuclear chromatin occurs in a fine network and in some areas nucleoli are prominent. Focally there is a variation in nuclear size and shape, and rare mitoses are seen. The intercellular stroma is fibrillar, acidophilic and contains lobules of hyalin material.

With van Gieson stain, fine intercellular collagen fibers are found in the section; with Masson's trichrome stain, the collagen is stained a lighter green than ordinary collagen.

A section of bowel at a distance from the tumor is negative except for a superficial peritoneal inflammatory reaction with polymorphonuclears and mononuclears cell infiltration and deposition of a granular basophilic debris.

A section through an area of mesenteric thickening shows organizing fibrinous exudate on the surface and organizing acute inflammatory process in the subjacent fibroadipose tissue.

DISCUSSION

Although characteristic of tumors of the small intestine, melena and prolonged unexplained anemia are not sufficiently specific to warrant other than a presumptive diagnosis. Nor is the X-ray diagnosis⁹ of lesions of the small bowel of sufficient accuracy to detect any more than a small number of these lesions, since their infrequency¹⁰ precludes specialized roentgenographic procedures as a routine measure. The occurrence of intestinal obstruction of undetermined etiology, or the occurrence of intussusception in an adult points strongly to the probability of a tumor of the small bowel.

In the case presented, the characteristic finding of prolonged melena and anemia (at times severe enough to require transfusion) and repeated mild to moderately severe episodes of intestinal obstruction, along with definite x-ray evidence of an obstructing lesion of the upper jejunum pointed to the diagnosis of small intestinal tumor.

SUMMARY

A case of isolated intestinal neurofibroma is presented with a brief review of the histogenesis, pathologic and clinical picture of this lesion.

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GASTRIC HYPERCHLORHYDRIA WITH THREE PRIMARY JEJUNAL ULCERS AND HYPOPROTEINEMIA

REPORT OF A CASE RELIEVED BY TOTAL GASTRECTOMY AFTER SUBTOTAL
GASTRIC RESECTION HAD PROVED INADEQUATE

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Hospital, Elmira, N. Y.*

The purpose of this communication is to report a case of multiple jejunal ulcer in which three separate perforations had occurred and in which the secretion of acid gastric juice was so excessive that free hydrochloric acid was found in the entire duodenum and upper jejunum. The high acidity of the content of the upper small intestine may well have been a major factor in the etiology of the jejunal ulcers and the underlying basis for a persistent and refractory hypoproteinemia. After 2 vagotomy operations and a subtotal gastric resection had failed, the tendency to ulceration was finally corrected by a total gastrectomy.

The literature on primary jejunal ulcer has been adequately reviewed by Morrin¹, by Ebeling² and more recently by Evert et al.³. The condition has seldom been diagnosed until perforation, obstruction or hemorrhage has made prompt laparotomy imperative or has led to necropsy. Little evidence has been adduced to support a "peptic"* etiology, or indeed any of the other theories advanced to explain its occurrence, such as infection, trauma and vascular abnormalities.

CASE REPORT

J. G., a 42 year old, white, male, water-plant filter operator, was admitted to the Surgical Service of this hospital on August 13, 1947, with the following history: He had first noted the onset of "indigestion" three years previously. One and a half years later he experienced a gnawing pain above the umbilicus one to two hours after meals, and occasionally at 2:00 A.M. It was relieved by food or alkali. Because of the recurring pain he was admitted to the Arnot-Ogden Hospital in Elmira, New York, six months later. There roentgen examination disclosed a constricted and scarred duodenal cap with retention of 75 per cent of the barium meal at the end of three hours. Gastric analysis, after a test meal, revealed values for free hydrochloric acid varying from 106 to 130, and for total acid, 124 to 147 clinical units. He was placed on an ulcer regimen, became free of distress and gained weight. The ulcer pain returned, however, about 11 months later, shortly after he had voluntarily discon-

* The term "peptic" is used to denote a penetrating process beginning in the mucosa and dependent on the destructive action of acid gastric juice.

tinued his dietary program. He was readmitted to the Arnot-Ogden Hospital, where roentgen examination revealed an irregularity of the mucosal pattern of the stomach, a deformed duodenal cap and dilatation of the third portion of the duodenum. The serum proteins were found to be low (3.5 gms. %). Following a period of intensive oral and parenteral protein administration, during which transfusions of plasma and blood were also given, he was scheduled for exploratory laparotomy. During the early hours of the morning on which operation was planned, he developed symptoms and signs of an acute surgical abdomen. At laparotomy, free fluid was found in the peritoneal cavity and three separate perforated ulcers were found in the first loop of the jejunum, within six inches of the Ligament of Treitz. The perforations were closed, after a small portion of the base of each was removed for biopsy. The stomach wall was thickened but there was no evidence of gastric or duodenal ulcer. The pathologist's report on the excised ulcer tissue was "typical peptic ulcer". The patient recovered from the operation but after a brief period of well being, began to vomit. Hypoproteinemia persisted despite intensive protein therapy and he was transferred to the Hospital of the University of Pennsylvania for further study and treatment.

On admission to this hospital he had no ulcer symptoms. He was a tall, thin, quiet and retiring individual of a fairly stable mental makeup, weighing 115 pounds. Detailed examination was negative except for a well-healed right rectus abdominal scar and slight pitting ankle edema.

The red blood count was 3.1 million cells with 74 to 88 per cent hemoglobin; white blood count varied between 5,900 and 7,000. The differential count was: neutrophils, 77 per cent; lymphocytes, 17 per cent; monocytes, 5 per cent, and eosinophils, 1 per cent. Sedimentation rate was normal.

Urinalysis revealed a specific gravity of 1.013, acid reaction, and no sugar, albumin, casts, white or red blood cells on repeated occasions. Serological tests for syphilis were negative. Microscopical examination of the stools for ova and parasites and for stainable neutral fat was negative. The cephalin cholesterol flocculation, thymol turbidity and colloidal gold liver tests were negative. Serum vitamin determinations revealed normal values for ascorbic acid (1.18 mg.%) and for vitamin A (41 mcg.%). That for carotene was slightly below normal (51 mcg.%). Serum calcium was 7.6 and 8.4 mg./100 cc.; phosphorus, 3.2 mg./100 cc., and total base, 146.8 milli. equiv. per liter. An oral glucose tolerance test revealed a diabetic type of blood sugar curve with a low fasting value. The values for blood sugar were: fasting, 59; at one-half hour, 168; at 1 hour, 222, and at 2 hours, 228 mg.%. The total serum protein values on admission were 3.7 and 4 gm./100 cc. with albumin values of 2.3 and 2.7 and with globulin values of 1.4 and 1.3 gms./100 cc. Blood volume (Evan's blue technique) was 5,000 and 5,660 cc., with hematocrit readings of 38 and 43 per cent. Basal metabolism was -13 per cent. He belonged to blood group B and was Rh-positive. An electrocardiogram revealed a normal tracing except for low and diphasic T-waves in the chest leads of a nonspecific nature. Fractional gastric analysis, employing oatmeal gruel as the test meal, revealed the following values: fasting, 41/64; at 30 minutes, 82/120; at 60 minutes, 66/106; at 75 minutes, 84/100;

at 90 minutes, 80/94, and at 120 minutes, 36/56 clinical units. Without stimulation the total volume of gastric juice aspirated in $2\frac{1}{2}$ hours was 1142 cc., its various fractions having a free acidity varying from 66 to 106 clinical units. Free acid was present in the entire duodenum and in the upper jejunum (Table 1). Dibutoline* (40 mg.), injected subcutaneously, decreased the average rate of gastric secretion from 8.8 cc. to 1.3 cc. per minute but did not decrease its acidity. The concentrations of bicarbonate, trypsin, amylase, esterase and lipase in separately aspirated (double-tube technique) fractions of duodenal content before and after stimulation with urecholine were normal.

Roentgen examination of the entire gastrointestinal tract was essentially negative except for marked alteration of the mucosal pattern of the stomach and small intes-

TABLE I

Titratable Acidity and pH of Fractions of Gastric, Duodenal and Upper Jejunal Fluid Obtained by Continuous Aspiration (Pre-Operative)

TIME INTERVAL IN MINS.	SITE OF ASPIRATION	VOLUME IN CC.	CLINICAL UNITS		pH
			Free Acidity	Total Acidity	
0-10	Stomach	120	76	90	1.1
10-20	Stomach	200	84	92	1.1
20-30	Stomach	98	80	90	1.15
30-40	Stomach	85	96	108	1.0
40-50	Stomach	74	102	110	1.0
50-60	Stomach	65	106	114	1.0
60-85	Stomach	120	66	80	1.2
85-116	Stomach	185	84	92	1.1
116-150	Stomach	195	80	90	1.15
150-160	Duodenum, 2nd	63	52	65	1.3
160-170	Duodenum, 2nd	102	62	72	1.28
170-180	Duodenum, 3rd	56	18	30	1.7
180-190	Duodenum, 3rd	31	22	30	1.65
190-200	Jejunum, upper	130	22	32	1.71
200-210	Jejunum, upper	12	18	30	1.72
210-220	Jejunum, upper	16	8	14	2.4
220-230	Jejunum, upper	4	8	14	2.5

tine. The abnormal small intestinal pattern had some of the characteristics ordinarily associated with sprue (Figs. 1, 2), but was thought to be due to edema of the bowel resulting from the marked degree of hypoproteinemia. The transit time for barium from stomach to cecum was approximately 5 hours.

Gastrosocopy revealed multiple erosions of the mucous membrane of the cardiac area of the stomach with organized blood clots adhering to the surface of the erosions. No other portion of the stomach was satisfactorily visualized because of resistance encountered to passage of the instrument beyond the cardia.

Because of the hypersecretion of highly acid gastric juice, the presence of free hydrochloric acid in the duodenum and first portion of the jejunum and the past history of perforation of jejunal ulcers, it was felt that some attempt should be made to decrease the gastric secretion in order to avoid further peptic ulceration. Further

* Dibutoline (Merck) is a choline ester with atropine-like action.

more, it was felt that a reduction in acidity in the upper small intestine might improve the digestion and absorption of protein and correct the hypoproteinemia.



FIG. 1. Roentgen appearance of stomach and upper small intestine on admission. The mucosal pattern and outline of the duodenal loop are grossly altered. There is puddling of barium in upper jejunum.

The procedure decided on was a subtotal gastrectomy combined with subdiaphragmatic vagotomy. Accordingly an intensive period of preparation for laparotomy was conducted during which a continuous intravenous drip of human serum albumin (66

grams daily for three days) was administered. At the end of three days, the total serum proteins were reported as 6.4 grams per cent. On the 29th hospital day, the



FIG. 2. Roentgen appearance of lower small intestine on admission. There is wide irregular segmentation of the barium meal with dilatation of segments in the ileum. The jejunum contains puddles of barium. The changes in the small intestinal pattern were thought to be due to a marked hypoproteinemia.

subtotal gastric resection, together with a subdiaphragmatic vagotomy, was carried out. Multiple vagus trunks were found anteriorly and only one, posteriorly. These were divided.

PATHOLOGIC REPORT

(Dr. R. C. Horn)

Gross Description: "The specimen consists of a portion of the stomach, 13 cm. across at the antrum and 23 cm. in length. The pylorus is not included. The serosa is markedly and uniformly injected except for the antral region which is paler. The rugae are prominent and pink with a finely mammillated surface. The antral portion is smoother and slightly paler. At four or five places there are small black areas, the largest 0.5 cm. in diameter on top of or between the rugae. They resemble old clotted blood and are on about the same level as the rest of the mucosa."

Microscopic: "Aside from edema and hyperemia probably resulting from the operation, significant changes are restricted to superficial hemorrhagic erosions of the

TABLE II

Titratable Acidity and pH of Fractions of Fluid Obtained by Continuous Aspiration from Gastric Remnant and Efferent Jejunal Loop of Gastroenterostomy after Subtotal Gastric Resection and Subdiaphragmatic Vagotomy on 17th Post-Operative Day

TIME INTERVAL IN MINS.	SITE OF ASPIRATION	VOLUME IN CC.	CLINICAL UNITS		pH
			Free Acidity	Total Acidity	
0-10	Stomach	42	44	52	1.42
10-20	Stomach	24	42	50	1.45
20-30	Stomach	90	42	52	1.4
30-40	Stomach	16	32	42	1.55
40-50	Stomach	40	22	30	1.78
50-60	Stomach	43	40	52	1.46
60-70	Stomach	55	40	54	1.4
70-80	Jejunum	35	0	6	6.5
80-90	Jejunum	10	0	6	3.8
90-100	Jejunum	3	—	—	—
100-110	Jejunum	32	12	24	2.0
110-120	Jejunum	90	10	26	2.12
120-130	Jejunum	74	0	16	3.5
130-140	Jejunum	23	0	10	4.1

mucosa, involving about one-fourth the thickness of the mucosa. Another finding of possible significance is the presence of fundal type glands down to the distal line of section as received in the laboratory. The three small segments of white cords labelled 'vagus nerves' consist of areolar tissue and nerve bundles."

Diagnosis: "Hemorrhagic erosion (multiple) of stomach mucosa. Heterotopic fundal glands of antrum of stomach. Vagus Nerve."

Following operation human serum albumin (66 grams daily for 5 days) and glucose were administered intravenously. Convalescence was uneventful. Large volumes of gastric juice drained from the Levin Tube. An intravenous insulin test performed on the 9th post-operative day was positive. The unstimulated secretion of gastric juice was 4.7 cc. per minute in contrast to 7.6 cc. per minute secreted pre-operatively. Intubation of the efferent loop of the jejunum revealed the presence of free hydrochloric acid in some of the samples, the values ranged from 0 to 12 clinical units (Table 2). Dibutoline (40 mg.), injected subcutaneously, decreased the average rate

of gastric secretion from 4.7 to 1.3 cc. per minute but did not decrease its acidity. The patient was discharged from the hospital on the 20th post-operative day and placed on a six feeding bland dietary regimen and 4 grams of non-absorbable antacid between meals and on retiring. During the ensuing 2 months, his weight increased from 115 to 145 pounds.

He was readmitted on December 1, 1947 (80th post-operative day) because of epigastric and para-umbilical pain of three weeks duration. It occurred 2 to 3 hours after meals and was partially relieved by food or alkali. Roentgen examination

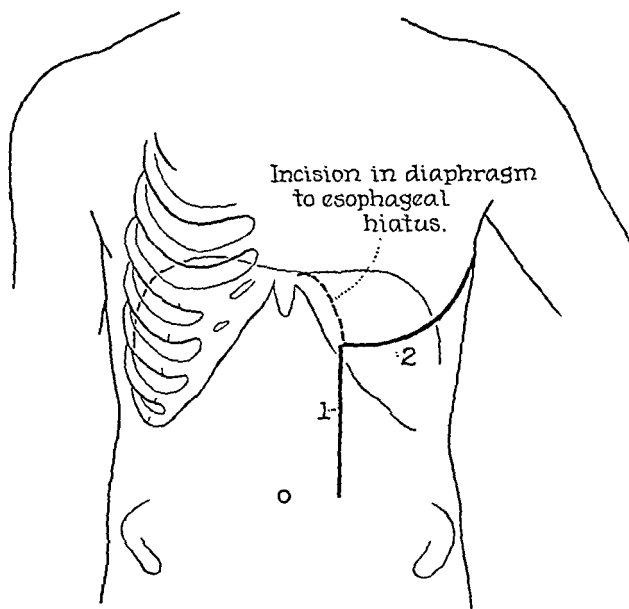


FIG. 3. Diagram illustrating extension of abdominal incision (1) across the costal arch (2). Broken line indicates incision in diaphragm.

revealed an ulcer on the jejunal side of the stoma. The serum protein value was 6.4 grams %.

In an attempt to obtain a more complete destruction of the vagal innervation of the gastric remnant and reduce acidity, a transthoracic vagotomy was performed on the 4th day of his second admission. Both main vagus trunks and all the intercommunicating branches that could be found were excised from the distal three-and-one-half inches of the thoracic esophagus. The dissection was carried all the way around the esophagus and down to the muscle. The patient recovered from this procedure satisfactorily. Subsequently the basal gastric secretion had a free acidity varying from 26 to 82 clinical units at a rate of 8.4 cc. per minute. The intravenous insulin test was again positive. The pain was not relieved; it increased in severity and penetration was suspected.

It was then decided to perform a total gastrectomy in order to remove all of the acid secreting area of the stomach. This was performed on the 19th day following the

to neutralize the tremendous amount of acid entering the duodenum. The low pH in the duodenum and jejunum was not favorable for maximum activation of the proteolytic enzymes. This provides adequate reason why protein digestion may have been inadequate. The resulting hypoproteinemia was probably responsible for the roentgen abnormalities noted in the mucosa of the gastrointestinal tract on the basis of edema, and for the low value for serum calcium on admission. The serum proteins and calcium had returned to normal by the time he was first discharged from the hospital.

SUMMARY

1. A case of primary jejunal ulceration, probable "peptic" in etiology, is presented. The secretion of acid gastric juice was so excessive that free hydrochloric acid was found in the duodenum and upper jejunum.

2. A low pH in the upper small intestine may well have been responsible for the hypoproteinemia as a result of the absence of a favorable pH for activation of proteolytic pancreatic enzymes. The hypoproteinemia was associated with a roentgen appearance suggesting edema of the mucosa of the entire gastrointestinal tract, especially the stomach and small intestine.

3. The gastric acidity was not reduced sufficiently by a subtotal gastric resection combined with subdiaphragmatic vagotomy or by a subsequent trans-thoracic vagotomy to prevent subsequent secondary jejunal peptic ulceration

4. Good health was eventually restored by a total gastrectomy.

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Editorials

MUCH NEW INFORMATION ON THE DYNAMICS OF THE HYPOGLYCEMIC REACTION

In a scholarly and thought-producing review article, Maximillian Fabrykant and Maurice Bruger (*Am. J. M. Sci.*, July, 1948), have summed up present-day knowledge in regard to the hypoglycemic reaction. Probably few internists realize how much work has been done to throw light on the mechanism of this reaction and how much more complicated it is than most men assume it to be.

For instance, it is not widely known that some persons fail to react to markedly lowered blood sugar titers, while others react violently to blood sugar values that are even above normal.

It has been shown that the respiratory quotient of the brain is about 1.0, which means that it derives its energy chiefly from carbohydrate. It is conceivable, therefore, that any lowering of the supply of glucose to the brain might cause serious disturbances in its metabolism. It has been shown that low blood sugar values are associated with diminished cerebral oxidation, and that the giving of glucose is followed by an increase in the use of oxygen by the brain.

There are a number of factors which will affect the hypoglycemic reaction. For instance, during anesthesia with veronal or luminal in rabbits, even profound hypoglycemia does not produce convulsions. Hypoglycemia can produce marked constriction of the cerebral arteries, arterioles and capillaries. Probably, for this reason, it can have an influence in an attack of migraine. According to Cobb and Lennox, the cerebral circulation is not impaired during hypoglycemia so long as there is no loss of consciousness.

More important than the level of the blood sugar seems now to be the way in which the brain reacts in order to control its consumption of glucose. It may be that the hypoglycemic reaction comes when the transfer of glucose from the blood to the brain is appreciably reduced, or when the brain is unable to use adequate amounts of the sugar supplied to it. Then there may be cerebral anoxia, or disturbances in the metabolism of acetylcholine.

There are other reactions which closely resemble the hypoglycemic one and which may have a different mechanism. For instance, cases have been described in which there were marked reactions due to hypoparathyroidism. When this disease was attended to, convulsions resembling those of epilepsy ceased.

Epinephrine also has something to do with the insulin reactions, and a deficiency in potassium may also play a rôle.

Severinghaus has suggested that the level at which hypoglycemic reactions occur is characteristic for the individual, but John showed that this level may vary in the individual from one day to another.

Joslin reported cases of typical hypoglycemic reactions in persons with a blood sugar between 220 and 290 mg. per 100 cc. of blood. John concluded that in nearly 50 per cent of insulin reactions the blood sugar was high.

Irreversible and fatal reactions from hypoglycemia have been observed. It is interesting that hypoglycemic reactions were known before the coming of insulin.

All of this does not mean that more diagnoses should be made of hyperinsulinism. Every thinking consultant knows that many such diagnoses made today are wrong. More careful study shows that the patients' spells are due to migraine or something else. Such spells do not come in the early morning and they do not clear away quickly with the taking of sugar. What this splendid review does is to show that the patient with what appears to be a hypoglycemic reaction should be studied much more carefully than often he now is. There are several things that may be wrong with him besides hyperinsulinism, and when he is having hypoglycemic reactions there may be contributing factors.

[W. C. A.]

THE NEWER ANTICONVULSANT DRUGS

Gastro-enterologists are coming to be more on the watch for equivalents of epilepsy. Quite a few of the patients who, without ulcer, complain of hunger pain or of peculiar attacks of abdominal pain, associated perhaps with nervous symptoms suggestive of a "storm" coming down the autonomic nervous system, can be found to have dysrhythmia in the electro-encephalogram and an occasional relative suffering from a convulsive disorder. Sometimes the patient can be helped by the giving of anticonvulsants, such as dilantin.

Today the sad feature of most of these cases is that the syndrome is not recognized soon enough and the patient has the abdomen explored once or twice to no purpose. Many a person of this type can be recognized quickly from the fact that he is so irascible. Occasionally he will be so irritable that he can hardly eat with other people at the table, and particularly with children who are making a disturbance.

Because of these facts, many gastro-enterologists and all internists should be interested in the fine article on anticonvulsants by James Toman and Louis Goodman in the October, 1948, number of *Physiological Reviews*. They give a bibliography of 216 titles, and discuss the relationships between the varying

structure of the several drugs and their anticonvulsant activities. They note that, recently, the glycerol moiety has been found by Kajdi and Livingstone, 1948, to give results equal to those of the ketogenic diet.

Unfortunately, the use of the new anticonvulsants must be watched carefully, because these drugs can cause serious and even fatal accidents. Sometimes combinations of two anticonvulsants can be used, such as a combination of dilantin and mebaral, or dilantin and phenobarbital.

It is good to know that already chemists have mapped out the directions in which a group of useful drugs are likely to be found.

[W. C. A.]

THE EFFECT OF GALACTOSE ON THE UTILIZATION OF FAT

In an article in the October 22, 1948, number of *Science*, Curt Richter reported a number of interesting experiments which show that galactose, given to rats, has much to do with their utilization of an otherwise pure fat diet.

On no food at all, 15 rats survived from three to six days. On galactose alone 13 rats survived from four to eight days and on oleomargarine 10 rats survived from nineteen to thirty-eight days. On oleomargarine and galactose together, 13 survived for from forty-seven to ninety-two days. Glucose added to the "oleo" diet failed to bring any increase in the survival times. When a small amount of "oleo" was added to galactose it had no effect in lengthening life. Deuel, Gulick and Butts (1932) found that the ingestion of galactose had a pronounced nitrogen-sparing action.

Richter suggested that possibly this peculiar action of galactose may be of value sometimes in solving some of the feeding problems of sick men and women.

[W. C. A.]

OBITUARY

Dr. Victor C. Myers

The death of Dr. Victor C. Myers of a heart attack in New York City on October 8, 1948 particularly disturbed his many friends for he had essentially no previous indications of illness.

Dr. Myers was well known for his work in clinical biochemistry and for his academic activities. The development of blood sugar methods and studies on digestive enzymes and on creatin, creatinin and pyrimidins and the chemistry of the blood interested him greatly. He was Professor of Biochemistry at Western Reserve University from 1927-46 when he became director of the Department of Clinical Biochemistry at that institution. A large number of graduate students were trained under his direction for teaching and research positions in his field.

Before joining the faculty at Western Reserve University, Dr. Myers had taught for 18 years; 2 years at Albany Medical College, 13 in the New York Post-Graduate Medical School and Hospital and 3 years as head of the Department of Biochemistry in the State University at Iowa.

Dr. Myers was an active member of the American Gastroenterological Association for many years and gave freely of his time by serving on committees and partaking in other activities of the Association. He was also a member of an imposing number of other scientific organizations including the American Society of Biological Chemists, the American Association for the Advancement of Science and the International College of Anesthetists.

He was born on April 13, 1883 in Bushirk Bridge, N. Y. He received the B. A., the M.A. and the honorary Doctor of Science degrees from Wesleyan University and the Ph.D. degree from Yale University in 1909.

His only near surviving relative is his wife Mrs. Marion Myers.

J. P. QUIGLEY

Book Reviews

OBESITY. *Edward H. Ryneerson, M.D. and Clifford F. Gastineau, M.D.* Charles C. Thomas, Springfield, Illinois. pp. 134. Price \$3.50.

This is an excellent and eminently sane discussion of the problems of obesity and of reducing patients who are overweight. The authors base their discussion on an enormous experience together with a thorough knowledge of the literature. The bibliography runs to 422 titles.

The authors feel that the only wise and logical method of reduction is with a balanced diet which contains few calories. If the patient takes less than the needed calories he will lose weight. If he takes more, he will gain. There is a short chapter on the psychotherapy of reduction and there is a very good discussion on the use of drugs. Recently the Council on Pharmacy and Chemistry of the American Medical Association stated that they now believe that amphetamine sulfate may be used in the management of obesity provided the dosage is held by the physician within proper limits. Ryneerson and Gastineau also feel that the drug is probably safe for most persons. However, there is some tendency to increase the blood pressure and occasionally to habituation; also, the drug can cause sleeplessness and nervousness. A number of other drugs have been tried. Hirsh (1939) felt that propadrine would be the best of these, but it would seem that the medical profession ought to avoid the use of all of them. If one gives a woman a drug to help her reduce, she is likely to try to depend on the drug alone. However, if it is strongly emphasized that it is diet only that will save her, she may stick to the diet. Patients should always have pointed out to them the fact that they will probably have to stay on the diet for the rest of their days, just as if they had a bad diabetes. It is no use bothering with these people unless they have intelligence, will power, and a strong resolve to get thin and stay thin.

There is a fine chapter on Diets for the Obese.

PSYCHOSOMATIC MEDICINE. *Edward Weiss, M.D. and O. Spurgeon English, M.D.* Second Edition. W. B. Saunders Company, Philadelphia and London. 1949. pp. 803.

This is an excellent book, containing as it does a tremendous amount of information. There are many helpful case reports. Excellent is the authors' plan of taking up the psychosomatic aspects of practice in the several specialties.

Some chapters have been rewritten and others were added to. This is a book every physician should read.

REGIONAL ILEITIS. By Burrill B. Crohn, M.D. Grune & Stratton, New York. 1949. Pages 229. Price \$5.50.

The logical person to write a monograph on regional ileitis was Crohn, who brought the disease to the attention of the medical world, and he has now done a splendid job. This book is well written and well illustrated, and the statements are all well documented. The greatest value of the book, of course, is that most of the statements are based on the tremendous experience of Doctor Crohn with this disease.

On page 131 Crohn notes what is very sad, and that is that everybody is now coming to realize that the recurrences following all types of surgery are frequent. As years pass after operation, more and more of the patients keep coming back with recurrences. They are doing this even 12 years after surgery. One in six patients returns with a recurrence shortly after leaving the hospital.

In a series of 222 cases of ileitis, primary section was done in 36, ileo-transverse colostomy with transection of ileum in 57, and ileo-transverse colostomy with transection followed by second-stage resection of lesion in 10 cases. There were five other cases in which the patient was operated on in different ways. In a series of 137 cases reviewed by Garlock and Crohn, the fewest recurrences were in the group with ileocolostomy with transection. The recurrence in that group so far has been 10.5 per cent.

Discussing the treatment of ileojejunitis on page 189, Crohn says penicillin is useless and streptomycin possibly of some avail. It is a question if the insoluble sulfonamides are of real value. They sometimes appear to control diarrhea for a while.

On page 114, Crohn says that obviously there is no medical treatment that will dissolve a fibrotic stenosis or will close a fistula that has developed. Lahey and Sanderson have said that there is no medical treatment worth consideration. The percentage of spontaneous cures is small, usually about 5 per cent. That certainly is not encouraging.

Although Crohn says that there would seem to be some rationale for the development of a conservative form of treatment, medical treatment can offer so little that the physician will usually be induced to call in the surgeon. He feels this way even when he knows how common the recurrences are after operation. Neither the medical nor the surgical treatment is satisfactory. Dr. Crohn is to be congratulated on a splendid achievement.

GERIATRIC MEDICINE: The Care of the Aging and the Aged. Second Edition, Illustrated. Edited by Edward J. Stieglitz, M.D. 1949. W. B. Saunders Company, Philadelphia and London. pp. 773. Price \$12.00.

This is the second edition of Dr. Stieglitz' monumental work on the care of the aging and the aged. There is more and more need for the study of geriatrics

now that the number of persons past sixty is increasing rapidly. This book is well written and is packed with information. The several chapters are written by different men, expert in their fields. The book has one serious defect and that is that the discussion of one of the most serious diseases of all those which afflict the aged, namely cerebral thrombosis, has been given only one page. The subject really ought to have a complete chapter devoted to it.

NEW AND NONOFFICIAL REMEDIES 1949. Issued under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association. J. B. Lippincott Company. Philadelphia, London, Montreal. 1949. pp. 805.

It is good to have a new edition of this valuable book. It is one that every physician should have within reach in his office. It is of particular value today when so many new drugs are being synthesized. Never in the history of the world have they come from the drug houses so fast. They come so fast that unfortunately a physician cannot become acquainted with them all.

MEDICAL ETYMOLOGY. *O. H. Perry Pepper, M.D.* W. B. Saunders Company, Philadelphia, London. 1949. pp. 263. Price \$5.50.

This is a labor of love by one of America's distinguished physicians and Professor of Medicine at the University of Pennsylvania. As Doctor Pepper says, this is not a dictionary, it is concerned more with the origin and derivation of words than with their meaning. In this book Doctor Pepper did not attempt to include all terms but only some 4,000 which are met with commonly. Doctor Pepper wrote this book because of his interest in words and in students.

The reviewer feels particularly sympathetic to the idea in the back of this book because when he was a small boy his father, a country physician, often took him for long rides, during which he trained him to recognize all the common Greek and Latin roots which have been compounded to produce the terms now used in science and medicine. This training was one of the most useful that the boy was to get in the course of his life. We thank Doctor Pepper for the good job he has done.

ABSTRACTS OF CURRENT LITERATURE

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STOMACH

HEBBEL, R. The topography of chronic gastritis in otherwise normal stomachs. *Am. J. Path.*, 25: 125 (Jan.) 1949.

In 72 per cent of 97 autopsies of patients free from manifest gastric disease, gastric lesions were found on microscopic examination. These lesions are more common in the older age groups. They did not uniformly involve the antrum and the body. Within each area, the lesions ranged from focal to diffuse in distribution. Diffuse antral gastritis was encountered in 8 per cent of the series and gastritis of the body in 14 per cent. Gastritic changes observed in conjunction with other gastric lesions must be interpreted in the light of the associated findings.

DAVID A. DREILING

SCHULMAN, J. JR., FALKENHEIM, M., AND GRAY, S. J. The phosphorus turnover of carcinoma of the human stomach as measured with radioactive phosphorus. *J. Clin. Invest.*, 28: 66 (Jan.) 1949.

The phosphorus turnover of tumors has been widely studied in animals and has been found to be higher than in normal tissues. Since no previous studies had been made on the turnover of phosphorus in naturally-occurring

human cancers, the authors undertook such an experiment related to carcinoma of the human stomach, this being one of the most common of malignancies. Nine patients were used; 3 were operated upon for duodenal ulcer, and 6 for malignant tumors. Radioactive phosphorus in neutral solution was administered intravenously about 36 hours before resection of the stomach. Within an hour after removal of the tissue, the mucosa from the stomach or duodenum or the cancerous tissue from the lesion was removed and prepared for analysis.

Total phosphorus, acid-soluble phosphorus, lipid phosphorus, and protein phosphorus were studied separately. It was found that the rate of phosphorus turnover is at least 45 per cent higher in the tumor tissue than in noncancerous tissue. For phosphoproteins, this rate is 124 per cent higher than normal; acid-soluble phosphorus turnover was essentially the same in cancerous and noncancerous tissue. The increased rate of phosphorus turnover is limited to the cancer tissue itself and is not demonstrable in the surrounding mucosa. In noncancerous stomachs, there is no difference in the rate of turnover in the areas where cancer is common, that is, there is no difference between

the pylorus and the greater curvature and the remaining portions of the stomach—nor is this rate increased in mucosa involved in atrophic gastritis, sometimes looked upon as a precancerous condition.

This work helps to clarify the manner in which cancerous lesions grow. Both anabolic and catabolic changes in cells are increased in the development and growth of a cancer but the anabolic process increases at a greater rate than the catabolic process, hence the growth continually grows larger. There is no actual difference in the phosphorus content of cancer or noncancerous tissue cells, but there is a difference in phosphorus turnover that has been demonstrated in these studies.

SAM OVERSTREET

PATTERSON, C. O., WILSON, F. W., HALEY, A. E., AND ROUSE, M. O. The diagnosis of lesions of the stomach. *Southern Med. J.*, 42: 19 (Jan.) 1949.

In a series of 321 consecutive patients studied by the authors in private practice and in a gastroenterologic out-patient clinic, 100 (34.2%) were found to have normal stomachs. The study included, besides a meticulous history and physical examination, gastric analysis, roentgen mucosal studies and gastroscopic examination. Malignant neoplasms were found in 60 cases (20.9%). Other conditions discovered were: Hypertrophic gastritis in 11.8 per cent, "atrophic mucosa" in 11.5 per cent, ulcer in 8.7 per cent, benign tumors in 3.1 per cent, diverticula and varices in 0.9 per cent each, and foreign bodies in 0.06 per cent. It is stressed that these figures are unusual, since most of the patients had been referred because of the strong suspicion of organic disease.

The paper is illustrated with roentgenograms and gastroscopic appearances of lesions. There are 12 case reports.

ANTHONY M. KASICH

DAVIS, R. E. AND IVY, A. C. Thermal irritation in gastric disease. *Cancer*, 2: 138 (Jan.) 1949.

The authors review the literature concerning hot foods as causative agents in peptic ulcer, chronic gastritis, and carcinoma of the stomach. Of these, although it is not clearly

established, the evidence is strongest for thermal carcinogenesis. The following mechanisms whereby thermal irritation may cause cancer are suggested: (1) Direct cellular alteration, (2) alteration in blood supply, (3) intrinsic formation of carcinogenic substances, (4) chronic irritation, and (5) removal of the normal protective mucous barrier. The authors have proposed a basis for study of the problem. They have defined oral temperature tolerance and temperatures of preference, established the approximate maximal intragastric temperature in the human, and determined the time and temperature factors necessary for the production of thermal gastric injury.

DAVID A. DREILING

BOWEL

BODIAN, M., STEPHENS, F. D., AND WARD, B. C. H. Hirschsprung's disease and idiopathic megacolon. *Lancet*, 256: 6 (Jan.) 1949.

This survey deals with 73 cases of megacolon, 39 of which were classified as true cases of Hirschsprung's disease, and 34 as idiopathic megacolon of unknown etiology. The clinical course is different in the two groups. In Hirschsprung's disease, the picture is that of chronic intestinal obstruction which develops a few days after birth. Acute flare-ups may occur from time to time. Abdominal pain is rare, however, the abdomen is enlarged. Active peristalsis may be seen or felt. The rectum is normal on digital examination, but a loaded sigmoid colon can be felt per abdomen or per rectum. The barium enema reveals the rectum to be of normal size. The sigmoid is narrowed for a distance of 1 to 12 inches. Proximal to this, it opens into a large dilated gas-filled colon by means of a funnel-shaped segment. In idiopathic megacolon, the constipation is present in mild form since birth, and is usually controlled by laxatives. Intestinal colic is frequent. There is difficulty in evacuation and the stools are large, hard and often streaked with blood. The rectum is loaded with feces. Barium enema in these cases reveals a distended rectum and pelvic colon to form a terminal reservoir or there is a tubular dilatation of a longer segment. The boundary between normal and abnormal bowel is poorly defined.

Neurohistological examination of autopsy and operative material in Hirschsprung's disease reveals a complete absence of parasympathetic ganglion cells from the intramural plexuses in the entire narrow segment and for a short distance into the dilated portion. The evidence favors congenital etiology. The latest treatment is rectosigmoidectomy in multiple stages. The rectum, the entire narrow segment and a portion of the cone-shaped funnel are excised preserving the anal sphincters. No histological abnormality has been discovered to explain the dilated colon in idiopathic megacolon. These cases are best treated by colon lavage and laxatives until all the fecal masses have been evacuated. The patient is then educated in normal bowel habits.

PHILIP LEVITSKY

KEYES, E. L. The occurrence of the gas stoppage sensation in acute obstruction of the ileum. *Surgery*, 25: 47 (Jan.) 1949.

The term "gas stoppage sensation," is used to describe the painful sensations located in the midabdomen associated with a downward urge not relieved by defecation or enemas. Six patients with surgically proven obstruction of the terminal ileum are presented. In 4 of these patients, the obstruction was produced by internal factors such as intraperitoneal bands or volvulus of the ileum, and in 2, the obstruction arose externally by strangulated inguinal or femoral hernias. In all 6 patients the gas stoppage sensation preceded the other classic symptoms and signs of obstruction of the small bowel. It preceded vomiting by from $1\frac{1}{2}$ to 24 hours, with an average of 10 hours.

The author credits Richardson with stating in 1932 that "pain of a cramp-like or continuous character persisting in spite of enema" is the essential symptom in acute obstruction of the ileum. The associated downward urge was later alluded to by Wangenstein and by Fitz. It is emphasized that the gas stoppage sensation occurs in both acute appendicitis before localization of pain in the right lower quadrant of the abdomen and in acute obstruction of the ileum. The conclusion is drawn that, when a patient presents the gas stoppage sensation,

a diagnosis of either of these two conditions can be suspected on an average of eight hours before vomiting develops. This earlier diagnosis can be converted to a lower surgical mortality by prompt relief of the obstructed ileum.

FRANCIS E. McDONOUGH

WEBBER, I. M. Cancer of the lower large bowel. *New Eng. J. Med.*, 240: 127 (Jan.) 1949.

This is a statistical paper reporting observations on a group of one hundred consecutive patients with carcinoma involving the rectum and rectosigmoid region. The pressing need for earlier recognition of this type of cancer is again emphasized. Results obtained, in terms of hospital deaths and survival rates, are recorded; fatal and significant, nonfatal complications are enumerated. Success obtained from a second resection in a very limited number of patients with recurrent or new cancer is noted. Although insufficient time has elapsed since treatment of the last patient to permit determination of the final figures on 5-year survivals, attention is called to the fact that the trend of the immediate postoperative hospital death rate is definitely downward.

ANTHONY M. KASICH

LESNICK, G. AND MILLER, D. Adenocarcinoma of the appendix. *Cancer*, 2: 18 (Jan.) 1949.

The authors analyze 17 cases of adenocarcinoma of the appendix. They conclude that these lesions are similar histologically to adenocarcinomas elsewhere in the large bowel, and display a similar progression and spread. In most instances, the malignancy has extended beyond the limits of the appendix by the time symptoms appear. Adequate therapy then entails a radical ileocelectomy. With less extensive resection the percentage of recurrence is distressingly high.

DAVID A. DREILING

OWEN, J. K. AND FINNEY, G. G. The surgical aspect of Meckel's diverticulum. *Southern Med. J.*, 42: 98 (Feb.) 1949.

The authors report 143 cases of Meckel's diverticulum, with a detailed analysis of the

embryologic, anatomic and pathologic aspects of the anomaly. They give a detailed description, with illustrations, of the surgical procedure of diverticulectomy. They conclude that Meckel's diverticulum is not always an innocuous anomaly, but may be the seat of many surgical conditions, some of which carry a high mortality. The diagnosis is often difficult. The sudden passage of a bloody stool by a young child, previously asymptomatic, is suggestive.

Complications related to Meckel's diverticulum are more often seen in children, and the mortality rate is higher, than in older patients. X-ray study is of little value. The surgeon can not tell from external inspection that the diverticulum is diseased; only histological study can exclude ulceration. In all doubtful cases of appendicitis when the appearance of the appendix does not explain the symptoms, a careful inspection of the terminal 4 feet of the ileum is necessary to rule out Meckel's diverticulum. The importance of this procedure is shown by the fact that 20 of the patients in this series had had from 1 to 3 laparotomies, and of these, 11 showed pathologic changes in the diverticulum at a later operation.

ANTHONY M. KASICH

MOSES, W. R. Reduction of mortality in intestinal obstruction. *Am. J. Surg.*, 77: 235 (Feb.) 1949.

A series of 223 consecutive patients with small intestinal obstruction, of whom 170 were subjected to operation, revealed a 6.3 per cent hospital mortality and a 6.5 per cent operative mortality. If the three cases of complete superior mesenteric artery occlusion are excluded, the operative and hospital mortality rates are 5.4 per cent and 4.9 per cent respectively. This represents an appreciable decrease compared with previously reported series. This improvement is principally attributable to: (1) Use of blood and plasma in large quantities, (2) careful timing of the operative procedure, (3) avoidance of the Miller-Abbott tube with its attendant false sense of security, (4) use of spinal anesthesia, (5) abandonment of exteriorization measures, (6) decisive and rapid operative repairs with the least possible trauma, and

(7) use of "physiologic" incisions which minimize postoperative adhesions, eviscerations and wound infections.

MICHAEL W. SHUTKIN

POSTLETHWAIT, R. W. Malignant tumors of the colon and rectum. *Ann. Surg.*, 129: 34 (Jan.) 1949

This report is an analysis of incidence, symptomatology, treatment and results in a group of 441 patients found at Duke Hospital between 1931 and 1945 to have malignant tumors of the colon and rectum. Fifty-seven per cent of the group were men. In slightly more than half of the patients, the lesion was found in the rectum. Approximately 5 per cent of the patients were under 30 years of age; 10 per cent were under 40 years. Symptoms had persisted for 6 to 8 months in most of the patients before hospital admission was sought. Of 84 patients with right colon lesions, 29 per cent had marked weakness and 23 per cent had felt an abdominal mass. Constipation and distention (as signs of obstruction) were three times as common in patients with lesions of the left colon as in those with lesions of the right colon. Abdominal pain was the most frequent first symptom in both right and left colon lesions. Where rectal and recto-sigmoid lesions existed, melena was the first sign in 80 per cent of the patients. From an examination of the abdomen, a mass was felt in 69 per cent of the lesions of the right colon, in 35 per cent of the lesions of left colon, and in only 7 per cent of the lesions of the rectum and recto-sigmoid bowel. The percentage of patients with hemoglobin of less than 9.0 grams was 13 for rectum and recto-sigmoid, 17 for left colon and 34 for right colon lesions. "Stool examination for occult blood was nearly always positive when done." Less than half the patients examined were deemed to have surgically resectable lesions.

LEMUEL C. MCGEE

BLEICHER, J. E. Cancer of the colon and rectum—A twelve-year survey of 142 cases in a general hospital. *Cancer*, 2: 25 (Jan.) 1949.

The author has surveyed 142 cases of carcinoma of the colon and rectum operated upon

during the past 12 years at a hospital in a city of 150,000 population in midwestern U. S. Of this number, 26.0 per cent were too far advanced for surgery and were treated with irradiation. Of the 104 cases subjected to exploration, 42 patients received only palliative treatment, with a mortality rate of 40.4 per cent. Sixty-two patients had a definitive procedure performed; the mortality rate was 29 per cent. Follow-up studies obtained on 91.2 per cent of the cases showed that 62.6 per cent of them died within the first year, 78 per cent by the 3rd year, and 94.4 per cent by the 5th year. These results emphasize the marked difference between statistics reported from the smaller hospitals and the large cancer clinics. Whether the discrepancy is due to the inability of the larger clinics to obtain satisfactory follow-up data on their cases or to a lack of specialized training and experience in cancer surgery in the smaller centers is difficult to determine.

DAVID A. DREILING

MCCREADY, F. J., BARGEN, J. A., DOCKERTY, M. B., AND WAUGH, J. M.
Involvement of the ileum in chronic ulcerative colitis. *New England J. Med.*, 240: 119 (Jan.) 1949.

A study is presented of 23 necropsy specimens of the bowel, in cases of chronic ulcerative colitis of the diffuse thrombo-ulcerative variety with ileal involvement, encountered at the Mayo Clinic from 1935 to 1946. In addition, the ileum in 6 surgically-removed specimens of bowel in cases of chronic ulcerative colitis with ileal involvement was studied. These 29 specimens were selected from 81 autopsy and 22 surgical specimens of the bowel in chronic ulcerative colitis in which certain proctoscopic and roentgenologic criteria were met.

The incidence of ileal involvement in the 103 cases was 28 per cent. The average length of ileal segment affected in the cases in which the pathologic changes were diffuse was 20 cm., with a range of 45 cm. In 7 of the 29 cases solitary ulcers were present, sometimes extending throughout the length of the small bowel. The nature of the disease in the ileum was similar to that found in the colon—essentially denuding and ulcerative. Twenty-two cases were diffusely ulcerative;

in 7, the ileum presented multiple solitary ulcers. Perforation of ileal ulcerations with generalized peritonitis was a very serious complication that occurred in 5 (17%) of the 29 cases. In 4 of these 5 cases, perforation occurred almost immediately after the performance of ileostomy.

The ileum is involved in chronic ulcerative colitis more often than is generally realized, and this should be borne in mind in examining all cases of diffuse chronic ulcerative colitis. Knowledge of the presence and extent of ileal involvement in chronic ulcerative colitis is an important consideration if surgical treatment is contemplated. Ileostomy for chronic ulcerative colitis, performed through a segment of ileum that is the site of ulcerative inflammatory changes, will probably produce a poor operative result. Perhaps this is one of the important causes of the high mortality associated with ileostomy in the treatment of this disease. Involvement of the ileum is probably also one of the factors that retard the healing process in the colon in chronic ulcerative colitis.

ANTHONY M. KASICH

LIVER AND GALL BLADDER

SPINK, W. W., HOFFBAUER, F. W., WALKER, W. W., AND GREEN, R. A. Histopathology of the liver in human brucellosis. *J. Lab. Clin. Med.*, 34: 40 (Jan.) 1949.

Specimens of livers in 11 patients with active brucellosis were studied. One patient died and 10 recovered. In all, there were hepatic lesions. The basic lesion was a granuloma, either in the liver lobule or in the portal areas. In several cases there was also a portal cellular infiltrate. The presence of the hepatic lesion had no relationship to the severity of the infection or to the clinical status of the patient. The granuloma was not considered to be specific for brucellosis; it could not be distinguished from lesions found in sarcoidosis, tuberculosis or syphilis. A battery of liver function tests was carried out simultaneously with the biopsy in 10 cases. In several, there was little or no deviation from normal, although definite histologic changes were apparent.

The authors suggest that biopsy of the liver be employed for diagnosis of doubtful cases of brucellosis. They also suggest that

brucellosis may play an important accessory role in the causation of cirrhosis.

EDGAR WAYBURN

POPPER, H., STEIGMANN, F., DYNIEWICZ, H., AND DUBIN, A. Use of thymol turbidity as lipid absorption test—Experiences with thymol turbidity and zinc sulfate turbidity tests under physiologic and pathologic conditions. *J. Lab. Clin. Med.*, 34: 105 (Jan.) 1949.

The authors performed the thymol turbidity and the zinc sulfate turbidity tests on blood specimens from 471 patients. Their findings confirmed previous reports that the thymol turbidity was elevated in acute hepatitis and less elevated in cirrhosis. They found it normal in patients with fatty livers with jaundice, slightly elevated in obstructive jaundice with no infection of the biliary tract, and more elevated when bacterial infection was also present. At times, elevation was found in diseases without apparent liver involvement, whereas a normal turbidity was occasionally found in patients with severe primary liver cell damage. The zinc sulfate turbidity was elevated in liver diseases and in inflammatory or malignant conditions generally, but was normal in extrahepatic obstructive jaundice. The zinc sulfate turbidity was especially high in cirrhosis.

Administration of various lipids raised the thymol turbidity. Fifty grams of butter with 6 grams of choline was the best mixture for this. The rise of the thymol turbidity paralleled that of the serum phospholipids. The rise after ingestion of fat was depressed in gastrointestinal diseases, obstructive jaundice and cirrhosis. It was suggested that the response of the thymol turbidity to fat ingestion may serve as a simple clinical test for intestinal absorption of fat.

EDGAR WAYBURN

WALTERS, W. AND PHILLIPS, S. K. Physiologic aspects of repaired stricture of the extrahepatic bile ducts: Report on 165 cases. *Proc. Staff. Meet. Mayo Clinic*, 24: 12 (Jan.) 1949.

Nearly all strictures of the bile ducts are the result of injury at time of operation. In 1940, Walters and Lewis reported a series of patients on whom the senior author had oper-

ated for benign stricture of the common bile duct during the previous 15 years. The mortality rate was 10 per cent. An additional 67 patients were operated on since then, excluding war years, with a mortality rate of 2.3 per cent. Some of these patients, of course, have had more than one operation for plastic reconstruction of the common bile duct. Choledochoduodenostomy and hepaticoduodenostomy were the operations commonly performed. Excision of the strictured part of the duct and anastomosis or plastic repair wherever possible is the desired procedure. A catheter, lying in the duct and anchored by means of a button on the skin, should be retained for 3-6 months in order to prevent contraction of the suture line. When ductal continuity cannot be established, an accurate choledochoduodenostomy gives the best result. Polythene tubes of the Mayo-Sullivan type are recommended instead of vitallium, because the latter often become plugged by bile salts and pigments.

FRANK NEUWELT

MACMAHON, H. E. AND THANNHAUSER, S. J. Xanthomatous biliary cirrhosis (a clinical syndrome) *Ann. Int. Med.*, 30: 121 (Jan.) 1949.

Histories of 5 cases of xanthomatous biliary cirrhosis, observed over a long period of time, are presented. The essential features of the syndrome are: (1) skin xanthoma; (2) hepatosplenomegaly; (3) obstructive jaundice of long duration; (4) blood cholesterol and lecithin values increased to 4-8 times normal concentration; (5) transparent serum with low lipid values. All patients were females; their ages were between 30 and 50 years. The onset of the disease is characterized by itching and slowly developing obstructive jaundice. The direct and indirect Van den Bergh reactions are positive; icterus remains unchanged throughout the disease. Xanthomata develop on arms, fingers, lower extremities, buttocks, and eyelids. Liver and spleen are enlarged, but ascites does not occur. Profuse hemorrhage from esophageal varices was the most common terminal event. Differential diagnosis from hemochromatosis is discussed.

Biopsies, taken during the early part of the disease, showed chronic inflammatory reac-

tion in the interstitial portal areas with blocking of the small bile ducts. On autopsy, the liver was found to be enlarged and without sign of extrahepatic obstruction, or of cholesterol deposits in bile ducts or gall bladder. Extensive fibrosis and fragmentation as well as regeneration of liver tissue, and evidence of active inflammatory reaction in interstitial tissue were observed. This form of cirrhosis is classified by the authors as "pericholangiolytic biliary cirrhosis". The etiology of the syndrome is discussed, and it is stated that its most important characteristic may be the increased generation of cholesterol and lecithin by the liver, simultaneous with impaired excretion of these substances.

L. T. ROSENTHAL

DOMENICI, T. J. Hepatitis without jaundice and without hepatomegaly. *New Eng. J. Med.*, 240: 88 (Jan.) 1949.

Four cases of hepatitis without jaundice and without hepatomegaly are presented. In each case, there was a sharply localized area of tenderness in the right upper quadrant toward the midline, associated with tenderness to jarring over the right lower thoracic cage. This finding was as significant as an enlarged liver and served as a reliable index to the clinical state. The clinical course was marked by exacerbations and remissions. These were characterized by varying degrees of anorexia, general malaise, and fluctuating intensity of right upper quadrant tenderness. Some exacerbations were accompanied by a rise in temperature. Anorexia was a constant and early symptom and was often severe enough to result in significant weight loss. Appetite and weight loss were only painstakingly regained. The long course makes subsequent chronic liver disease an eminent possibility. The cephalin-cholesterol flocculation seemed to be most sensitive and reliable index of both the liver function and the clinical course.

ANTHONY M. KASICH

THORLAKSON, P. H. T. Injuries to the bile ducts—their prevention and repair. *Can. Med. Assoc. J.*, 60: 119 (Feb.) 1949.

The author discusses in detail the problem of injuries to the bile ducts, following operation on the extra-hepatic biliary apparatus, with

particular reference to their recognition and treatment. Increased safety in gall bladder disease is considered to depend upon earlier operative intervention. Patients should not be allowed to undergo repeated attacks of biliary colic. The importance of good surgical technique, adequate exposure and visualization of the anatomic structures, and the use of proper preoperative and postoperative measures is again emphasized. Immediate repair of injuries to the bile ducts is preferable. However, if immediate restitution is not possible, provision should be made for repair in the early postoperative period. Various surgical techniques are described in detail.

JOSEPH B. KIRSNER

MCNEIL, D. L. The symptomatology of liver disease. *Can. Med. Assoc. J.*, 60: 140 (Feb.) 1949.

The symptoms of hepatic disease are reviewed with reference to the gastrointestinal, cardiovascular, genitourinary, hematological, endocrine and nervous systems. They have also been considered in relation to disturbances in protein, fat and carbohydrate metabolism. It is again emphasized that tests of hepatic function measure certain biochemical changes occurring during the course of hepatic disease. They may be of value in (1) recognition of latent disease of the liver; (2) differential diagnosis of symptoms of possible hepatic origin, such as ascites, upper gastrointestinal hemorrhage or edema; (3) differential diagnosis of jaundice; (4) determination of liver injury secondary to biliary obstruction; (5) following the course of jaundice; and (6) detecting residual damage to the liver and continued activity of hepatic disease.

JOSEPH B. KIRSNER

PANCREAS

WELLS, C. A. AND ANNIS, D. Experimental pancreaticogastrostomy. *Lancet*, 256: 97 (Jan.) 1949.

In an attempt to establish a safe procedure for the transplantation of the pancreas into the alimentary tract, in patients undergoing operation for carcinoma of the ampulla of Vater or head of the pancreas, the following experiment was performed. In 7 dogs, the tail of the pancreas was separated from the

head and implanted into the stomach. In one of these animals, the implant was made in the fundus, and in the other 6, the pyloric portion was used. The dog with the fundus implant died of acute hemorrhagic pancreatitis. Of the remaining 6 dogs, 1 died, on the 51st postoperative day, of anemia and malnutrition. Pyloric pouches were made containing the pancreatic implant. Secretin was injected intravenously and pancreatic juice collected. Normal amounts of amylase were found. The remaining 4 animals were sacrificed on the 15th, 45th, 49th and 66th postoperative days. Histological sections showed firm union between the pancreas and stomach. The pancreatic duct was continuous with the gastric mucosa.

The operation of pancreatico-gastrostomy is feasible in dogs. Whether it can be applied to humans is questionable since the anatomy is not quite the same in the two species.

PHILIP LEVITSKY

MENTEN, M. L. AND KINSEY, W. C. Asymptomatic retention of pancreatic secretion. *Arch. Path.*, 47: 90 (Jan.) 1949.

Sections of pancreatic tissue removed from 256 young people were studied. Thirty-five sections showed retention of eosinophilic secretion in the pancreatic acini. None of the patients had clinical evidence of cystic fibrosis of the pancreas. The causes of death of these patients varied so widely that it was impossible to detect an agent responsible for the retention.

GEORGE A. BOYLSTON

ANEMIAS

JONES, E., TILLMAN, C. C., AND DARBY, W. J. Observations on relapses in pernicious anemia. *Ann. Int. Med.*, 30: 374 (Feb.) 1949.

In 12 patients with pernicious anemia who had received adequate amounts of liver extract, this treatment was experimentally discontinued. Amount of medication during the year preceding the experiment was 420-1020 units, and, on the average, a dose had been given at intervals of 3 to 4 weeks. Six patients (50%) experienced relapse within 8 to 18 months after discontinuation of therapy. The criterion for relapse was the finding of two or more successive counts with a drop of

more than two times the standard deviations below the mean RBC count for the year preceding cessation of liver extract. The 6 patients who showed no relapse remained from 26 to 29 months without liver extract. Fecal urobilin was determined after the method of Watson, and an increase of over 300 Ehrlich units was noted in the 6 patients prior to clinical relapse, indicating increased hemolysis. There were no neurological manifestations in any of the twelve patients observed. This is in contrast to reports of high incidence of neurological manifestations of patients receiving pteroylglutamic acid. Only an incomplete hematological response was obtained following administration of pterioic acid, a part of the pteroylglutamic acid molecule. Administration of pteroylglutamic acid was followed by an initial good response, but relapse occurred while under treatment. Higher urobilin values were found in the stools of pernicious anemia patients in relapse, and such increases were first observed when anemia was only marginal.

L. T. ROSENTHAL.

ULCER

AMENDOLA, F. H. The management of massive gastroduodenal hemorrhage. *Ann. Surg.*, 129: 47 (Jan.) 1949.

The author urges that the term "massive hemorrhage" be restricted to instances of rapid loss of blood of such proportions as to cause unmistakable hemorrhage shock. Such bleeding, when associated with an ulcer, is "invariably arterial in origin," usually from erosion of the superior pancreaticoduodenal or the right or left gastric arteries or their major branches.

Between 1943 and 1947, 120 patients with massive gastroduodenal hemorrhage were admitted to the Roosevelt Hospital in New York City. Eighty-five were treated expectantly with 13 deaths (15 per cent). All but 2 of the fatalities were in patients over 45 years of age. There was but 1 postoperative fatality in 11 patients who were operated upon within 48 hours of admission. The remaining 25 patients were treated surgically between the 3rd and 21st day after admission and form a group too heterogeneous for analysis.

If the bleeding patient, over 50 years of

age, does not show a satisfactory rise in blood pressure with repeated transfusions in the first 24 hours, he should receive surgery. A recurrence of massive bleeding in the older ulcer patient demands immediate blood replacement and operation. Patients, who are first seen after many days of severe continuous or intermittent hemorrhage, are poor surgical risks and should be treated expectantly. In any bleeding patient, if a surgeon experienced in gastric problems is not available, "it is more prudent to accept the hazard of expectant treatment." Partial gastrectomy with excision of the ulcer is the procedure of choice. Occasionally it is necessary to leave the base of a deeply penetrating duodenal ulcer. If a source of bleeding is not found after thorough inspection of the stomach and duodenum (through gastrotomy and duodenotomy), closure without resection is advised.

LEMUEL C. MCGEE.

WELCH, C. E. AND ALLEN, A. W. Gastric ulcer—a study of the Massachusetts General Hospital cases during the ten-year period 1938–1947. *New Eng. J. Med.*, **240**: 277 (Feb.) 1949.

Several trends in the management of gastric ulcer have become apparent in the past few years. It has been shown that the term "peptic ulcer" should be eliminated, and that gastric ulcer is a distinct entity not to be confused with duodenal ulcer. It has also been demonstrated that gastric ulcer still cannot be differentiated from cancer in nearly 10 per cent of the cases. Although improved diagnostic methods have tended to reduce this error, the mortality of operation has simultaneously declined to minimum levels. To the surgeon interested in cancer control, these tendencies make gastric resection advisable for all gastric ulceration. The physician, on the other hand, is tempted to treat these ulcers medically, stressing the operative mortality, the discomforts of operation and the postgastrectomy symptoms that may appear.

If medical therapy is elected, cases must be carefully selected, studied by the best radiologist and gastroscopist available, and followed vigilantly, with early recourse to surgery if healing is not prompt. The physi-

cian must realize that new operative technics provide satisfactory excisional surgery for ulcers of the cardia and that radical surgery for hemorrhage, the most common complication of gastric ulcer, is both safe and desirable.

From the principles outlined above, it appears that surgical therapy is indicated in approximately 75 per cent of the patients with gastric ulcers and that excellent results are to be expected after gastric resections.

ANTHONY M. KASICH.

FOGELMAN, M. J., GROSSMAN, M. I., AND IVY, A. C. Further studies on the effect of continuous intragastric infusion of acid and pepsin in dogs. *Surgery*, **25**: 60 (Jan.) 1949.

Previous work demonstrated that continuous intragastric infusion of 0.10 N HCl produced acute perforating gastroduodenal ulcers in dogs within 40–90 hours. These animals developed a concurrent metabolic acidosis. When acidosis was prevented by maintaining a normal blood pH with parenteral NaHCO_3 , ulcers did not develop.

This report deals with the results of continuous intragastric infusion of HCl solution to which has been added 0.2 per cent pepsin. Three groups of dogs were used. In the first group, metabolic acidosis was not controlled and all dogs developed peptic ulcer similar to those produced by 0.10 N HCl alone. In the second group of dogs, the acidosis was controlled by parenteral 0.16 N NaHCO_3 and gastroduodenal ulcers did not develop. In the third group of animals, the strength of the continuous intragastric infusion was increased to 0.15 N HCl but the pepsin concentration remained at 0.2 per cent. Acidosis was prevented by increasing the strength of the parenteral NaHCO_3 to 0.30 N. Fifty per cent of these animals developed either gastric or duodenal ulcerations. Because the peptic activity of 0.10 N HCl-pepsin solution is the same as 0.15 N HCl-pepsin solution, the ulcerogenic activity of the latter must be due to the increased acid concentration alone. This is contrary to Le Veen's theory that the ulcerative action of acid-pepsin solutions is mainly dependent upon their peptic activity.

FRANCIS E. McDONOUGH.

ROSSIEN, A. X. Treatment of gastroduodenal peptic ulcers with protein hydrolysate and a nonreactive aluminum hydroxide preparation. *Rev. Gastroenterol.*, 16: 34 (Jan.) 1949.

To gain the added protein intake and yet offset the secretagogue effect, the author devised the plan of using a nonreactive aluminum hydroxide gel 1 hour after giving protein hydrolysate. One-half ounce of the latter in milk was given 2 hours after meals and 2 teaspoonsful of the alumina gel containing $\frac{1}{4}$ grain sodium phenobarbital and $\frac{1}{16}$ grain atropine sulfate was given 1 hour and 3 hours after meals. On the basis of treating 15 patients for 21-40 weeks, the author feels the results indicate that this regimen has merit and further investigation is being carried out.

C. WILMER WIRTS, JR.

THOREK, P. Surgical therapy in gastroduodenal ulcer. *Rev. Gastroenterol.*, 16: 53 (Jan.) 1949.

On the basis of the author's experience in performing 63 vagotomies (with 47 added after the paper was presented), it is felt that this operation is indicated in duodenal and stomal ulcer which do not respond to medical treatment. Gastric ulcers, however, should not be treated by vagotomy. The transabdominal approach for this operation has distinct advantages in that the lesion may be inspected and a gastroenterostomy performed to compensate for obstruction or atonic complications. Further observation of the treated cases is indicated before a final conclusion can be drawn as to efficacy of this procedure.

C. WILMER WIRTS, JR.

RICKETTS, W. E., PALMER, W. L., KIRSNER, J. B., AND HAMANN, A. Achlorhydria and peptic ulcer: A further study of the role of peptic activity in the pathogenesis and course of peptic ulcer. *Ann. Int. Med.*, 30:24 (Jan.) 1949.

This paper represents a study of the incidence of ulcer in acid and non-acid stomachs, and the effect of achlorhydria on the course of peptic ulcer. In 500 consecutive cases with duodenal ulcer, the maximum histamine response was in excess of 40 clinical units.

Occasionally duodenal deformity, due to scarring, was noted in the presence of pernicious anemia or gastric cancer associated with achlorhydria, but active duodenal ulcer was not seen in such cases. In 170 cases of gastric ulcer, hydrochloric acid was invariably found upon examination; however, the maximum free acidity after histamine stimulation remained under 20 clinical units in 20 patients. No recurrent jejunal ulcer was seen after partial gastrectomy in cases where the pH was over 4.0. Two case reports are presented where spontaneous achlorhydria occurred in patients with a history of recurrent duodenal ulcer of over 10 years' standing. There were no exacerbations after achlorhydria had occurred. Two case histories of gastric ulcer are presented, in which prolonged achlorhydria was induced by X-ray irradiation. All these ulcers healed and did not recur when it was possible to maintain achlorhydria for more than 3 months, regardless of the age of the patient or the duration of the disease. The duodenal ulcers in a group of 102 patients healed in all but 3 cases, in which achlorhydria was maintained less than one month. Two illustrative case reports are presented. In conclusion, the authors state that peptic ulcer is encountered only in the presence of acid gastric secretion.

L. T. ROSENTHAL.

ALLEN, A. W. The differential diagnosis in gastric ulcer. *Rev. Gastroenterol.*, 16: 13 (Jan.) 1949.

The author feels that gastric ulcer is primarily a surgical lesion. From his own experience 14 per cent of the cases thought to be benign proved, on pathologic study, to be cancer. Other reports showed the same error in about 10 per cent of cases. In 5 per cent of cases, benign ulcer was found when malignancy was suspected. Location and size of the lesion, age, duration of symptoms, and absence of free acid are factors, in addition to the results of roentgen and gastroscopic study, that may help in evaluating a gastric ulcer. Small ulcers in young patients can be treated medically but these patients must be carefully followed. Persistence of ulceration or apparent recurrence should be looked with suspicion. Hospital treatment will lead to better evaluation of the problems

than ambulatory treatment. The results of surgical treatment in benign gastric ulcer may often be better than conservative measures. If surgery is undertaken, resection of the distal stomach including the ulcerative lesion should be performed. Vagus nerve resection has no place in this treatment.

C. WILMER WIRTS, JR.

RIVERS, A. B. The treatment of gastric, duodenal or jejunal peptic ulcer. *Rev. Gastroenterol.*, 16: 18 (Jan.) 1949.

Treatment of peptic ulcer is governed by etiologic factors and correct diagnosis. Clinical history and observations should be evaluated accurately and complications recognized. Of paramount importance is the decision as to treatment. Although preliminary medical treatment of gastrojejunal ulcer is justifiable, the indications, in the end, are surgical. The author does not wish to appear dogmatic in the statement that treatment of gastric ulcer is always surgical. He states that there may be cases in which a few weeks' trial of medical treatment is warranted, to be followed by roentgenologic, gastroscopic and clinical observation.

Uncomplicated duodenal ulcer usually is a medical problem. Indications for surgical intervention are: (1) failure of the ulcer to heal under adequate medical care; (2) acute, subacute or chronic infection; (3) pyloric obstruction; (4) repeated massive hemorrhage; and (5) associated disease of the gallbladder or the appendix. An adequate regimen includes mitigation of the acid factor and establishment of normal resistance; it consists of frequent feedings of nonirritating, acid-binding food, containing all elements in proper proportions. Antacids are given between feedings. Antispasmodics and sedatives are prescribed as required. Drastic restriction of food intake for prolonged periods is seldom necessary. A palatable, adequate bland diet is allowed within 8-10 days. Some dietary precautions, with supplementary feedings, are continued for 6-12 months.

Prerequisites for surgical and medical prevention of recurrences are control of gastric acidity, maintenance of normal resistance of tissue and treatment of constitutional diathesis. The patient must be made to under-

stand the physiologic and psychodynamic aspects of recurrences and must cooperate in their prevention.

L. T. ROSENTHAL.

FAXON, H. H. AND SCHUCH, W. G., JR. Gastrojejunocolic fistula. *New Eng. J. Med.*, 240: 81 (Jan.) 1949.

Gastrojejunocolic fistula, the most serious complication of gastrojejunostomy, has become less common since gastric resection has replaced the former operation in the surgical treatment of peptic ulcer. Gastrojejunal ulcer is the inevitable precursor of a gastrojejunocolic fistula. The frequency of postoperative ulceration varies according to different authors, from 3 to 51 per cent. The period of freedom from symptoms, in the 9 cases studied by the authors, varied from a few months to 30 years, and the time elapsing between gastroenterostomy and the development of fistula varied from 5 to 30 years.

Fistulas may be gastrocolic, jejunocolic or gastrojejunocolic. They are almost always single, varying in size from a few mm. to 6 cm., and are lined with smooth mucous membrane, with no ulceration. The colon is often constricted at the lesion with partial obstruction and dilatation. The large jejunal folds act as a valve that prevents the passage of gastric contents into colon via the fistula, but permits regurgitation of feces and flatus into the stomach. The diarrhea, avitaminosis, hypoproteinemia and loss of weight are probably due to irritation of small intestine by feces and not to direct passage of gastric contents into the colon.

Clinically, weight loss was the most frequent symptom, occurring in 8 of 9 cases. Diarrhea, weakness, nausea and vomiting, hematemesis, anorexia, fecal eructations, foul breath and abdominal pain were other clinical manifestations. Definitive treatment is surgical, after preliminary therapy to restore the patient to sufficiently good nutrition to withstand the formidable attack on the fistula itself. Blood transfusions, parenteral fluids and chemotherapeutic agents are of vital importance. At times, these supportive measures will be insufficient and the vicious cycle perpetuating the diarrhea must be broken. This is usually accomplished by an ascending colostomy as a procedure pre-

liminary to corrective surgery. Surgery on the fistula itself consists either of simple closure of a small fistula, excision of the fistula and gastroenterostomy stoma, or the removal en bloc of the area of the stomach, jejunum and colon involved in the fistulous process with restoration of normal continuity of the gastrointestinal tract. Finally the ulcer itself must be dealt with, and while gastric resection is a good operation, it is uniquely difficult.

ANTHONY M. KASICH.

PROCTOLOGY

WAUGH, J. M. AND KIRKLIN, J. W. The importance of the level of the lesion in the prognosis and treatment of carcinoma of the rectum and low sigmoid colon. *Ann. Surg.*, 129: 22 (Jan.) 1949.

The relation of the location of rectal and low sigmoid cancers to survival was studied in 388 patients undergoing abdominoperineal resection for adenocarcinoma at the Mayo Clinic between 1931 and 1940. Patients whose lesions lay within 5 cm. of the anal margin had a poorer 5-year survival rate (66 per cent) than did patients whose lesions were 6-10 cm. above the anal margin (75.5 per cent survival) or those whose lesions were 11 cm. or more above (68.1 per cent survival). When the analysis was limited to lesions showing grade 2 (Broders) malignancy, the trend was more clear-cut: 0-5 cm. above anus yielded a 61.1 per cent 5-year survival rate; 6-10 cm., 74.5 per cent; and 11 cm. or more, 75.0 per cent.

The authors think it unlikely that there is any inherent variation in the malignancy of adenocarcinoma at varying levels of the bowel. It is believed that the differences in curability of the low-lying lesions are due to spread of the neoplasms along the lymphatic channels passing laterally from the lesions, accompanying the middle hemorrhoidal vessels and lying along the levator ani muscles.

LEMUEL C. MCGEE.

LEVENE, G. A new method for the roentgenologic study of the rectum. *Surgery*, 25: 68 (Jan.) 1949.

By using the technic and new apparatus described for coating the rectum with a thin

deposit of barium suspended in water, roentgenographic study in detail is possible. The author states this technic has been used in 100 patients, and he furnishes illustrations of roentgenograms taken in 5 patients with chronic proctitis, chronic ulcerative colitis, annular carcinoma, cauliflower carcinoma and sessile polyp located in the rectum. The procedure is obviously safe, attended by no discomfort and apparently extends satisfactory roentgenographic examination of the large bowel to include the rectum.

It is emphasized that this technic does not supplant digital and proctoscopic rectal examinations but it does allow the roentgenologist to diagnose lesions in an area that previously he could only poorly visualize. It is claimed that small ulcerations on the superior surface of Houston's valves can be demonstrated by this technic when they cannot be seen through the proctoscope. An additional contribution is the opportunity to study in detail the normal anatomy of the rectum without disturbing its normal physiology. The report of such a study is in press.

FRANCIS E. McDONOUGH.

BRAASTAD, F. W., DOCKERTY, M. B., AND DIXON, C. F. Melano-epithelioma of the anus and rectum. *Surgery*, 25: 82 (Jan.) 1949.

Ten cases of melano-epithelioma of the anus and rectum, encountered at the Mayo Clinic prior to April 1947, are reported in detail. Two of these cases had been previously reported so that 8 are added to the literature on this subject, resulting in a grand total of 94 reported cases from all sources. The incidence of melano-epithelioma is said to be 0.25 per cent of anorectal neoplasms and about 1 per cent of all epitheliomatous lesions in this location. Analysis of all the reported cases is undertaken and the results can best be presented in the authors' own summary. "These lesions almost always occur in the vicinity of the dentate line, are frequently pedunculated, tend to be small and are often covered by normal-appearing mucosa. They probably arise from melanoblasts of the anal epithelium, and location of the tumor in the rectum may be due to submucosal spread from the anus. Symptoms are generally produced early, and the diagnosis of "polyp"

or "carcinoma" is frequently made on proctoscopic examination. Prognosis is uniformly bad, regardless of the type of therapy, there being only 3 known "cures" in the entire group of 94 patients."

FRANCIS E. McDONOUGH.

SURGERY

SCOTT, W. J. M. AND SCHILLING, J. A. A critique on vagotomy, part II: The contemporary use of vagotomy. *Am. J. Dig. Dis.*, 16: 1 (Jan.) 1949.

The current status of vagotomy is reviewed, and the authors stress the fact that any opinion about this operation is still based on a relatively short period of observation. Comment is made upon the immediate results of vagotomy on ulcer pain, gastric motility and secretion, and note is made of the relatively low incidence of failures reported in such series as those of Dragstedt, Moore, and Grimson. In discussing the incidence of failures, important statements are made regarding the psychological evaluation of patients prior to vagotomy and emphasis is placed upon avoidance of this operation in patients whose personality is not of the so-called "classic ulcer type."

The authors emphasize the need for complete vagotomy. Although they have used a transabdominal approach, they believe that the lower esophagus must be thoroughly mobilized so that the vagus trunks can be divided at a high point and the lower esophageal plexus carefully removed. The operation advised, therefore, is a supra-diaphragmatic one, even though the approach is transabdominal. They believe that vagotomy should be combined, in a majority of instances, with either gastroenterostomy or pyloroplasty, in order to avoid obstructive complications after vagotomy. These operations should be more widely used in patients who have partial stenosis. The value of vagotomy is stressed, not only in the treatment of jejunal ulcer, but also in the treatment of duodenal ulcer when this has been characterized by a long history of ulcer symptoms with alternating periods of activity and remission.

As contraindications to vagotomy the authors list acute hemorrhage, acute per-

forations and sub-perforations, complete pyloric obstruction with metabolic imbalance, gastric ulcer, and the presence of ulcer in psychopathic individuals.

Final comment is made on the need for prolonged follow-up in the study of vagotomized patients and also upon the confusion which will result if no attempt is made to distinguish patients whose vagotomies have been technically satisfactory from those in whom the operation has been incomplete.

HENRY TUMEN.

LAHEY, F. H. Further experiences with injured bile ducts. A new method of repair.

New Eng. J. Med., 240: 161 (Feb.) 1949. Experiences in the surgical management of 227 patients with benign strictures of, or injuries to, the bile ducts are presented. The development of the different methods employed since the publication of a previous report in 1923 is outlined, and the disadvantages of all these measures are discussed. A new plan, which has been employed for a minimum of 5 years in 43 cases, results in preservation of the sphincter of Oddi and direct mucosa-to-mucosa anastomosis, when it can be employed. It offers a logical approach to the surgical management of this currently discouraging lesion, and the prospect of permanent discharge of bile from the liver into the duodenum without complications that are prevalent with other procedures.

ANTHONY M. KASICH.

PEARSE, H. E., RADAKOVICH, M., AND COGBILL, C. L. An experimental study of antiperistaltic jejunal loops. *Ann. Surg.*, 129: 57 (Jan.) 1949.

Three types of surgery were applied to dogs in order to determine the optimum length of an antiperistaltic loop of bowel—such as required in the Whipple operation for carcinoma of the head of the pancreas in order to provide a new entrance for the bile—for the prevention of regurgitation of intestinal contents. The experimental study was directed toward the problem of prevention of cholangitis from regurgitation of intestinal contents in patients whose gallbladder or common duct is anastomosed to a jejunal segment.

In the Roux-Y type of anastomosis, regurgitation occurred for a distance of 10 inches in the antiperistaltic segment of the jejunum opening through a permanent stoma in the abdominal wall. The optimum length for such a segment in the dog was found to be 12 inches. This length prevented regurgitation of dye, barium and intestinal contents out of the stoma. Longer loops resulted in peptic ulcer formation.

The experimental surgical procedures are described and illustrated diagrammatically.

LEMUEL C. MCGEE.

PHYSIOLOGY: SECRETION

NOBLE, R. L. The stimulation and inhibition of gastric secretion in cats by barbiturate and thiourea derivatives. *Can. Med. Assoc. J.*, 60: 55 (Jan.) 1949.

The effect of 80 barbiturates, thio-barbiturates and thiourea derivatives on gastric secretion was studied in unanesthetized cats with permanent gastric fistulae. Ethyl -3,3- dimethylallyl barbiturate and ethyl -1,3- dimethyl-1-butenyl barbiturate caused a profuse gastric secretion, the volume and acidity being as great or greater than that evoked by histamine. (1-methyl-butyl) ethylacetyl thiourea inhibited the stimulating effect of insulin without causing any other untoward effect. Other substances did not inhibit such secretion unless given in doses large enough to cause ataxia or anesthesia. The commonly used barbiturates were without effect on gastric secretion until near anesthetic doses were used.

JOSEPH B. KIRSNER.

METABOLISM AND NUTRITION

JANOWITZ, H. D., HANSON, M. E., AND GROSSMAN, M. I. Effect of intravenously administered glucose on food intake in the dog. *Am. J. Physiol.*, 156: 87 (Jan.) 1949. Daily intravenous administration of glucose to dogs accustomed to a standard diet had no noticeable influence on the food intake during periods of 2-9 days. The maximum glucose given was 400 cc of a 20 per cent solution.

ARTHUR E. MEYER.

ANATOMY

JACKSON, R. G. Anatomy of the vagus nerves in the region of the lower esophagus and the stomach. *Anat. Rec.*, 103: 1 (Jan.) 1949.

The operation of vagotomy for peptic ulcer has revived interest in the precise anatomical distribution of the vagus nerves both above and below the diaphragm. In 50 cadavers, an anatomic study was carried out on the vagus nerves in their course below the pulmonary plexus and their distribution to the stomach. Surprisingly, older anatomists disagreed on several vital points relative to vagus distribution to the stomach, but did agree that both anterior and posterior vagal trunks contain fibers from both right and left vagal nerves, that gastric branches of both anterior and posterior trunks are distributed mainly along the lesser curvature of the stomach, and that branches leave the anterior trunk just below the diaphragm and pass through the gastrohepatic omentum to the liver. The authors found 4 types of anterior and posterior trunks: Type A became single above the diaphragm and passed through the diaphragm as a single trunk; type B became single above the diaphragm but divided into two or three trunks before passing through the diaphragm; type C became single at the diaphragm; type D was never single above the diaphragm. The vast majority of both anterior and posterior vagal trunks belonged to type A. In the majority of cases, communicating branches were found between the nerve trunks about the diaphragm. The distribution of the hepatic branch of the anterior trunk and the coeliac branch of the posterior trunk is described.

FRANK NEUWELT.

MISCELLANEOUS

LOCKWOOD, J. S., YOUNG, A. D., BOUCHELL, McL., BRYANT, T. R., JR., AND STOJOWSKI, A. J. Appraisal of oral streptomycin as an intestinal antiseptic, with observations on rapid development of resistance of *E. coli* to streptomycin. *Ann. Surg.*, 129: 14 (Jan.) 1949.

Stools were cultured before and after the institution of oral streptomycin, in 24

patients receiving streptomycin alone, and in 9 patients receiving this antibiotic combined with sulfathalidine. Particular attention was paid to the colony counts for coliform organisms, streptococci and clostridia. The reduction in intestinal flora was unpredictable and incomplete. In the patients receiving oral streptomycin alone, approximately one-half showed no lowering of the coliform colony counts. In the group having lower counts, the response was not prolonged beyond the fourth day in one-half of the responsive cases (one-fourth of the treated series). Only 12 per cent of the patients had a temporary reduction in the streptococci content of the stool. The effect on the counts for clostridia was likewise inconstant. Where sulfathalidine was combined with streptomycin, the results were essentially similar to those obtained by oral streptomycin alone.

In several patients, who showed an early favorable response to the efforts for suppression of intestinal flora, the organisms rapidly developed resistance to streptomycin. The authors conclude "its use in the preoperative preparation of surgical cases is not to be recommended."

LEMUEL C. MCGEE.

ALPERT, S. AND MARTIN, G. J. A comparative study of the inhibitory action of chemical agents on peptic activity. *Am. J. Dig. Dis.*, 16: 10 (Jan.) 1949.

An outline is presented of studies on the inhibition of pepsin action through the use of physical and chemical means. A large number of substances were investigated. It was found that the specific inhibitory power of an insoluble polyamine resin was increased by the addition of small amounts of sodium alkyl sulphate. Peptic activity was also inhibited by such substances as charcoal, alumina, calcium phosphate, various proteins and proteoses, and colloidal aluminium hydroxide. The mechanisms responsible for pepsin inhibition may be either surface absorption, mass action effect of end products, or chemical interaction with the formation of new compounds. It is also assumed that other mechanisms, not yet understood, may exist.

HENRY TUMEN.

WOLD, L. E. AND BAGGENSTOSS, A. H. Gastro-intestinal lesions of periarteritis nodosa. *Proc. Staff Meet. Mayo Clinic*, 24: 28 (Jan.) 1949.

Thirty cases of periarteritis nodosa were autopsied between the years of 1926 and 1946 and clinical signs and symptoms were correlated with postmortem findings. Abdominal pain, loss of weight and anorexia were found in over half of the cases; vomiting, abdominal distention, melena and nausea were also found with decreasing frequency. In 18 cases, symptoms referable to the gastrointestinal tract were present and autopsy disclosed lesions in the abdomen. In 5 other cases, gastrointestinal symptoms were present but necropsy failed to disclose any evidence of periarteritis nodosa within the abdomen. In 3 cases, necropsy revealed periarteritis of the gastrointestinal tract but no clinical signs or symptoms had been present. In 4 cases, neither clinical nor postmortem evidence of periarteritis nodosa were present. In 21 cases, autopsy disclosed macroscopic lesions of the gastrointestinal tract including hemorrhages and infarcts. Infarcts and hemorrhages accounted for all the intra-abdominal lesions except for peritonitis and fat necrosis of the pancreas. Microscopic examination showed hemorrhagic infarcts in various stages of healing and repair. In some cases the vascular lesions were confined to arteries of one size; in other cases, vessels of all size were affected. Any portion of the gastrointestinal tract may be involved by periarteritis nodosa, including liver, gall-bladder, pancreas, and mesentery. Even though abdominal pain was the most frequent physical symptom, autopsy failed to disclose any involvement of the abdominal viscera in 5 of the 21 cases in which abdominal pain was so marked.

FRANK NEUWELT.

WALTERS, W. Differential diagnosis of acute surgical conditions of the abdomen. *Penn. Med. J.*, 52: 361 (Jan.) 1949.

The age and condition of the patient, the duration of abdominal symptoms, and the progress since the onset of symptoms are of the greatest importance in making a differential diagnosis of the particular type of

acute abdominal condition that exists. Exploratory operation is advisable when the nature of an intra-abdominal lesion remains in doubt. A scout X-ray film is frequently of great aid in the diagnosis of acute conditions.

In many patients, who are desperately ill and in whom it appears as though a surgical procedure would end fatally, exploration may disclose an operable lesion and the patients may be cured. The use of aids to the

surgeon such as antibiotics, improvements in anesthesia, control of anemia and shock by blood transfusions, intestinal intubation to effect decompression, have made surgery feasible in desperately ill patients. Cecostomy or transverse colectomy is preferable to tube drainage of the intestine when an obstructing lesion is in the large bowel, and when medical measures, such as repeated enemas, do not relieve the obstruction.

CHARLES A. FLOOD.

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LIVER FUNCTION IN CHRONIC ALCOHOLIC PATIENTS

II. CORRELATION BETWEEN ELEMENTS OF THE HISTORY AND PRESENCE OF LIVER DYSFUNCTION AS INDICATED BY LABORATORY TESTS

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A previous publication¹ presented a study of 300 chronic alcoholic patients from the better classes of society who had been admitted to a private institution for the treatment of alcoholism. A number of liver function tests‡ had been performed on each of the patients and the presence and degree of liver dysfunction was arbitrarily designated on the basis of the tests.

The series of patients was arranged in groups according to the severity of liver dysfunction found, as follows: Group 1. Those with no or minimal liver dysfunction (78 patients or 26.0% of the series). Group 2. Those with slight but definite liver dysfunction (160 patients or 53.3% of the series). Group 3. Those with moderate to severe liver dysfunction (62 patients or 20.7% of the series).

This communication will correlate the presence of liver dysfunction with certain elements of the individual anamnesis, the presence of which are thought to be just cause for suspecting liver disease in both alcoholic and non-alcoholic patients.

RESULTS

Sex. The number of female patients included in the study was too small to be susceptible to statistical analysis. Examination of the collected data did not disclose any tendency for the appearance of liver dysfunction in either sex.

Age. The patients varied in age from 23 to 69. It has become axiomatic that the older the patient, the greater the incidence of portal cirrhosis. Yet, the oldest age group in this series exhibited *less* than the expected incidence of disturbed function, while patients under 45 exhibited *more* than the expected incidence of liver dysfunction. Although this trend is too slight to be of statistical significance, the evidence appears quite convincing that liver disturbances

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‡ The determinations used were: One minute and total serum bilirubin, serum cholesterol and cholesterol esters, serum protein and A/G ratio, prothrombin time, serum alkaline phosphatase, cephalin-cholesterol flocculation, thymol turbidity and flocculation, quantitative urinary urobilinogen, bromsulphalein retention, hippuric acid synthesis and galactose tolerance.

in alcoholic patients of the type included in our series, do not become more frequent or severe with increasing age—in fact, the opposite might be true to some extent.

Length of Drinking history. The length of time a patient drank excessively might be expected to correlate roughly with his age and such is the case in this study. In the group with the shortest drinking history, the incidence of normal liver function is somewhat smaller, i.e., there is a greater incidence of disturbed function than would be expected. The remaining groups fail to show findings suggestive of any trend in either direction. The data certainly do not support any idea that liver dysfunction is more frequent in those patients with the longer alcoholic history.

Periodical versus steady drinking. There appears to be a definite tendency to more frequent and severe liver dysfunction among steady than among periodical drinkers, although the trend is not sufficiently marked to be completely significant statistically.

Type of liquor consumed. There is no apparent relationship between the frequency or severity of liver dysfunction and the alcoholic proof content of the beverage habitually consumed. Those who drank whiskey (as a rule undiluted) and those who rarely drank other than beer or wine had almost exactly the expected incidence of normal and abnormal liver function.

It might be expected that the meticulous drinker, who confined his consumption to a single type of beverage—beer, wine or whiskey—might suffer less hepatic impairment than the alcoholic who would drink anything with alcohol in it. However, a marked trend, of statistical significance, was discerned which showed a *greater* incidence of liver dysfunction in the “single type” drinker, when compared to less discriminating individuals. We were unable to find less liver dysfunction in those who drank only bonded liquor. Also, these data suggest that the congenetics of a specific liquor are innocent of inciting liver dysfunction.

Nationality. The data fail to indicate any correlation between the principal extraction of the patient and the presence of liver dysfunction. Comparatively few of the group were of pure descent and only those were chosen for comparison who possessed a dominant racial characteristic.

History of previous jaundice. Twenty-seven patients of the group gave a history of previous jaundice, apparently unrelated to the alcoholic history, which had occurred from 2 to 40 years prior to the present study. No trend toward the presence of liver dysfunction in the group with antecedent liver disease was found. Eleven of the 27 cases with a history of jaundice had been so afflicted during the period of excessive drinking. Of these 11 patients, 2 were classified in Group 1, 7 in Group 2 and 2 in Group 3. This distribution, while not amenable to statistical analysis, is not noticeably different from that

seen in the group of patients who had been jaundiced prior to the onset of alcoholism, or in the series as a whole.

History of delirium tremens or alcoholic convulsions. There was a slight trend toward the occurrence of more frequent and severe liver dysfunction in patients who have never had delirium tremens or alcoholic convulsions than would be expected. The trend is not sufficiently marked to be statistically significant.

Previous chronic disease. Forty-seven patients in the series gave a positive history of previous chronic disease of sufficient duration to suggest a possible causative relationship to liver dysfunction.

The small amount of data available for evaluation suggests that the entire group with previous serious chronic disease shows a slight tendency (of no statistical significance) to more severe and frequent liver dysfunction. Certain diseases (peptic ulcer, arthritis, rheumatic fever and syphilis) appear to be most frequently accompanied, or followed, by deranged liver function. This interpretation must be made with great caution because of the small number of cases considered. Thirteen patients with allergic diseases showed the expected distribution among the various groups with normal and disturbed liver function.

Changes in tolerance for alcohol. Among alcoholics, the statement that liquor can no longer be tolerated in the same amount as previously is commonly encountered. In our group of patients about 50% had noted this phenomenon. On the other hand, about 17% had noted an increased tolerance and the remainder had observed no change. When this element of the history is correlated with the results of liver function studies it was found that those with no change in tolerance showed about the expected distribution while among those with notable changes there was a pronounced trend toward a greater incidence of liver dysfunction in those with *increased* tolerance and of normal function in those noting *decreased* tolerance. This trend is statistically significant and the most marked of any encountered in the study.

Many alcoholics state that alcohol has a different effect than formerly. For instance, during the pre-alcoholic period a few drinks caused a feeling of exhilaration or well-being; now the same amount of alcohol causes severe depression, nervousness, belligerence or other unpleasant states. About two-thirds of the patients in this series had noted such a definite change in the effect of alcohol and one-third had not. When this symptom was correlated with the presence of liver dysfunction no trend was found to indicate that this symptom depends upon any disturbance of the liver brought to light by the laboratory procedures used in this study.

A third common symptom presented by the seasoned drinker is alcoholic amnesia, often called a "blackout." This differs from "passing out," in that consciousness and apparent normal behavior is retained by the patient al-

though he has no memory of events or his actions during the period. A trend (of possible statistical significance) is seen in the data which however, is toward the presence of liver dysfunction in those experiencing no alcoholic amnesia and normal liver function in those with amnesia.

Nutrition. The dietary habits of the patients of this series were established by careful questioning. One hundred and twenty-eight were found who consistently ate well and 122 who consistently ate poorly. When the dietary history was compared to the results of laboratory tests no apparent relationship was found to exist between the presence of liver dysfunction and good or poor "dietary habits."

Occupation. When occupation is divided into classes according to the amount of physical work done there is a very slight tendency to increased incidence of liver dysfunction among those with sedentary employment and less in those performing medium or heavy work. It was found that those working in a "healthful" outdoor environment had slightly increased tendency to liver dysfunction than did those with inside jobs.

Eighteen of the patients worked in contact with hepatotoxic agents. There was no definite increase in the rate with which liver dysfunction was encountered in this group.

The number of patients occupied in specific jobs is too few to be susceptible to statistical evaluation. Certain occupations, however, such as bartenders (12 patients), salesmen (31 patients) and professional people (10 patients) appeared to have more than their share of liver dysfunction while office workers, engineers, machinists and farmers appeared to have less.

Changes in sexual potency. Impotence among alcoholics may vary from loss of libido to loss of ability and may be most marked either when sober or when drinking. Seventy-six of the male patients in this series had this complaint while 155 had noted no definite change and 11 had believed their sexual powers to be increased. The average age of those with impotence was 44.6 and for those with no change 50.7. The patients with impotence had a slightly higher incidence of moderate liver dysfunction than expected but since these same patients showed less than the expected incidence of severe liver dysfunction, a clear-cut trend is not established. Among the females in the pre-menopausal age group, it was found that slightly more than half suffered from menorrhagia and metrorrhagia. The mean age of the two groups was 37.6 and 37.0 respectively. While the data were not sufficient to evaluate statistically, no apparent tendency for those with menstrual abnormalities to possess more marked degrees of liver dysfunction appeared.

DISCUSSION

It should be recalled that the patients comprising this series were from the better classes of society and were treated at a private hospital for alcoholism,

not for other diseases to which alcoholism was incidental as is the usual case in county or charity hospitals. Most studies on the relation of alcohol to portal cirrhosis have been done on patients with cirrhosis by determining how many were also alcoholic. Our investigation is different. We have selected known alcoholics and have attempted to determine the incidence of portal cirrhosis among them, thus the results of our studies might be expected to be different from those of others for this reason.

The data reported in the first of this series of papers, which dealt with the results of liver function tests, has shown that while liver disturbances are common in alcoholic patients, the profile of liver function studies obtained usually was not characteristic of portal cirrhosis. On the basis of these observations it was postulated that portal cirrhosis was no more common in chronic alcoholics of the type studied by us than in the population at large.

Throughout the paper the term "liver dysfunction" has been used in preference to "liver damage" as we are by no means convinced that the abnormalities found were the result of irreparable destruction of hepatic tissue as seen in portal or biliary cirrhosis.

The absence of any correlation between the presence of liver dysfunction and advancing age, or longer periods of drinking, is inconsistent with the concept of alcohol, or the syndrome of alcoholism, causing permanent and progressive liver damage. In our group of patients, the incidence of liver dysfunction is not greatly different in the younger and older age groups; in fact it suggests a favorable state of affairs in the older age group and in those with the longest drinking history. If it is argued that the older patients might drink less than the younger, then it must be conceded that the dysfunction is temporary, reversible and susceptible to improvement with improvement in the drinking habits. Such improvement is not usually seen in patients with proven portal cirrhosis whether they drink less or, in fact, abstain altogether.

At first thought, the increased incidence of liver dysfunction in the steady drinker might be attributed to a greater alcohol intake from year to year or to less favorable nutritional states. However, the preceding data indicate that the total amount of alcohol consumed by the individual is not the sole factor. Likewise, subsequent data strongly suggest that nutritional factors are not of primary importance. The most reasonable explanation is the previous assumption that the liver dysfunction induced by alcohol is temporary and reversible, and that recovery during the abstinent phases of the periodical alcoholic may account for the decreased incidence of liver dysfunction in the periodical drinker. Such a theory would necessitate casting alcohol in the role of an inciter of temporary liver dysfunction. It is well known that alcohol may have a specific effect in promoting the deposition of fat in the liver. It is also believed that dysfunction secondary to fatty metamorphosis of the liver is temporary and reversible. This logically leads to the suspicion that the characteristic

liver dysfunction seen in chronic alcoholism is the result of fatty degeneration of the liver rather than portal cirrhosis and is in agreement with the findings of Chalmers² who noted that 16 of 24 chronic alcoholic patients presented the histological appearance of fatty metamorphosis of the liver. Whether fatty degeneration of the liver predisposes to the subsequent appearance of portal cirrhosis has never been proven. It should be possible for the two conditions to exist concurrently, uninfluenced by each other, and each dependent upon quite different etiological factors.

There is no readily apparent reason why the group characterized by indiscriminate drinking of any and all types of alcoholic beverage should show less hepatic impairment than those who drank only a single type. The absence of any discernable differences between those habitually drinking but a single type of liquor (whether it be beer, wine or whiskey) strongly suggests that the congenics of any particular liquor are innocent of inciting liver dysfunction. The same is true for chance contamination of alcoholic beverages by metals such as copper from beer dispensing apparatus or other toxic impurities. The fact that the connoisseurs of our group, who drank only bonded liquors, were as frequently and severely afflicted with liver dysfunction as those of less discriminating taste indicates that the presence of higher alcohols, aldehydes, etc. in cheaper grades of whiskey did not predispose to the development of hepatic disorders.

Most studies (in experimental animals) suggest that previous hepatic injury makes the liver susceptible to an hepatotoxic effect from ingestion of alcohol. Thus, a classical experiment is the demonstration of hepatic cirrhosis following feeding of alcohol to an animal suffering from acute hepatitis (arsenic, carbon tetrachloride chloroform). That such does not always occur in humans is suggested by the following protocol:

Case 61. This patient, 34 years of age, was discharged from the Army in 1943 because of chronic hepatitis following homologous serum jaundice contracted 12 months previously. At the time of discharge the patient was jaundiced and bromsulphalein retention (dose unknown) was 25%. The history of alcoholism existed prior to induction into the army and excessive drinking continued uninterruptedly both before and subsequent to the appearance of jaundice, until his admission to the hospital in October 1947. He had received no treatment for chronic hepatitis during the interim. Preliminary liver function studies revealed as the sole abnormalities, bromsulphalein retention 8.0% using a dose of 5 mg/kg with 45 minute reading, 1 minute serum bilirubin 0.42 mg and total serum bilirubin 2.7 mg. When repeated 1 year later there were no abnormalities in any of the function tests.

That the severe liver dysfunction attendant upon alcoholism does not condition the liver to greater susceptibility to subsequent disease is suggested by the following protocol.

Case 170. This patient, 44 years of age, was hospitalized in December 1947 for acute and chronic alcoholism. On physical examination the liver was greatly enlarged, the abdominal veins were engorged and prominent and moderate ascites was present. There was marked edema of both feet and secondary anemia with hemoglobin 56%. Laboratory studies revealed 1 minute and total bilirubin 2.6 and 5.6 mg per 100 cc respectively. Total serum protein was 5.4 gms with reversal of the A/G ratio. Alkaline phosphatase was 7 units and quantitative 24 hour urobilinogen output was 22 mg. Bromsulphalein retention was 78%. The hippuric acid synthesis was less than normal (0.77 gm). The values for total cholesterol, cholesterol esters and galactose tolerance were normal. The cephalin cholesterol flocculation was negative at 24 and 48 hours and the thymol turbidity and flocculation reactions were normal. The patient was given blood transfusion and routine treatment for liver dysfunction. Within 60 days all liver function tests had returned to normal. Then the patient again became jaundiced, this time manifesting positive serum flocculation tests and a profile of function studies characteristic of homologous serum jaundice. The episode of acute hepatitis ran an uneventful course, all liver function tests again returning to normal where they have remained in spite of the fact that he resumed drinking. The clinical picture on admission in this patient was that of severe portal cirrhosis. The subsequent course is not that of portal cirrhosis. Liver biopsy on admission revealed "marked fatty metamorphosis with some slight increase of fibrous tissue in the area of the portal trinity regions." There is no evidence that within 12 months following the original observation portal cirrhosis had become more marked in spite of a severe acute insult to a liver severely deranged as a result of chronic alcoholism.

The data concerning 10 other patients who had been jaundiced during the period of excessive drinking show that not one had developed serious liver disturbances by the time they were examined during this study (from 1 to 20 years after the jaundice). A conclusion that continued excessive ingestion of alcohol before, during and after an acute episode of liver disease does not predispose to the development of subsequent morbid changes is difficult to escape.

It has been suggested that delirium tremens and alcoholic convulsions might occur because of a failure of the liver to detoxify alcohol in the normal manner or because of the accumulation of theoretical toxic substances in the body. The finding of *better* over-all liver function in those with a history of delirium tremens or convulsions would tend to discount such a theory. This theory might still be reconciled with our data, however, by postulating the selective loss of some as yet undescribed liver function, for which we did not test, which exerts its effect primarily in maintaining the health of the central nervous system. If so, it must be recognized that the loss of such a theoretical function could not parallel the loss of other known functions or else the livers of patients with delirium tremens must recover much more rapidly than the others.

While there appears to be a tendency for prolonged chronic illness to be accompanied by more frequent and severe liver dysfunction, this trend is so

slight that it probably is not influenced by the fact that the patients were alcoholic. If alcoholism had been of importance a much stronger trend would have been anticipated. Aside from liver dysfunction, the presence of chronic disease in this group of 300 patients was remarkable by its infrequency. Hypertension of moderate degree was found in only two of this series. Not a single clear-cut case of cholelithiasis or cholecystitis was found. One patient had submitted to drainage of the gallbladder 6 years previously. He was vague as to his symptoms or what was discovered at laparotomy. A second patient had submitted to cholecystectomy 2 years previously with an equally vague history of symptoms and whether gallstones had been found. Nearly all the patients with chronic disease susceptible to cure or arrest were not suffering from the illness at the time of admission.

Many theories attempting to explain the diverse symptomatology of chronic alcoholism have arisen from the fact that following absorption, ingested alcohol passes first through the liver and is there supposedly altered considerably in its chemical form. Hepatic disease has been said to result in a decreased rate of alcohol oxidation and consequent decrease in the individual's "tolerance" to a given quantity of alcohol. The results of our study throw but little light upon such hypotheses for we were unable to find evidence of hepatic dysfunction being more marked or frequent in those suffering from decrease in tolerance for alcohol. Nor were the abnormal reactions noted following alcohol imbibition seen predominantly in those with liver dysfunction. Any discernible trend, surprisingly, is toward normality in those noticing decrease in tolerance or delirium tremens and abnormality in those without such changes or with increased tolerance. Apparently the integrity of liver function does not have any bearing upon the genesis of these symptoms, although, as previously suggested some hitherto unknown or undescribed function of the liver, which was not tested during this study, might be deranged.

It has been well shown that nutritional deficiency is a factor of great importance in the etiology of portal cirrhosis. The results of our study were, therefore, surprising for they showed that the type of hepatic disturbance encountered among our alcoholics was not more frequent among those with the poorest dietary habits. Since those of our patients with poor dietary habits were probably no better off nutritionally than many alcoholics seen in charity hospitals, the absence of any definite trend toward the presence of liver dysfunction in those of our patients with the poorest dietary history again raises serious doubt in our mind that the dysfunction was caused by portal cirrhosis.

Occupational factors failed to show any marked effect on the presence of liver disturbance. The slight tendency to increased hepatic dysfunction in those working in an outdoor environment might be explained on the basis of greater food consumption with more fat in the diet, but if such an explanation

is accepted it would tend to identify the hepatic dysfunction with fatty degeneration rather than portal cirrhosis.

In classifying patients who had occupational exposure to hepatotoxic substances, the exposure was presumed but in no instance was exposure to toxic concentrations proven or even suspected. It appears that normal contact with such known hepatotoxins as carbon tetrachloride (dry cleaners), formaldehyde resin fumes (plywood workers), lead and volatile hydrocarbons (gasoline handlers), arsenic sprays (orchardists), etc. does not predispose to increase liver disturbances in chronic alcoholic patients.

In portal cirrhosis, the liver is supposedly unable to inactivate female sex hormone, thus accounting for impotence and the feminization seen in male patients. While the specific function of destroying estrogen was not tested during this study, it is apparent that liver function as a whole was not unusually disturbed in our patients complaining of impotence, or in the females with menorrhagia. As a consequence it must be presumed that impotence among our patients was not secondary to liver disease and therefore should not be considered as clinical evidence of portal cirrhosis.

SUMMARY

The original purpose of this section of the study was an attempt to select certain factors in the history and symptomatology of alcoholic patients which might be of value in predicting the likelihood of liver dysfunction being present in any given case. In this the study has been a failure because the absence of clear-cut trends and the paucity of significant statistical differences indicate that not a single factor which we considered was of great importance in this respect. However, the study has been revealing in that it has shown that there is no tendency toward the presence of more serious or frequent liver dysfunction in those patients in the older age groups or with the longer drinking history. This is taken as evidence that alcohol, or the syndrome of alcoholism, does not predispose to the development of any progressive degenerative disease of the liver such as portal cirrhosis. The slight tendency for less frequent and severe liver dysfunction to be present in periodical alcoholics, as compared to steady drinkers, suggests that the characteristic type of liver dysfunction seen in chronic alcoholism is reversible and susceptible to improvement during the abstinent phases of the periodical alcoholic. This again suggests that the process is not portal cirrhosis.

Certain symptoms seen in chronic alcoholic patients such as changes in tolerance or response to alcohol, delirium tremens or sexual impotence appear to be independent of the presence or absence of liver dysfunction.

Finally, the results of this study certainly indicate that the ingestion of alcohol, even in excessive amounts, before, during and after an episode of

acute hepatitis does not necessarily predispose the liver to serious or irreversible damage.

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EXPERIMENTAL OBSERVATIONS ON CARDIOSPASM IN MAN

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It has repeatedly been demonstrated that the various levels of the gastrointestinal tract participate in protective bodily reactions to a variety of noxious stimuli including emotionally charged situations. Studies to date have concerned chiefly salivary function¹⁻⁷, gastric function^{1, 8, 9, 10}, and the functions of the colon¹¹⁻¹³. Considerable evidence has been presented, however, that the esophagus too is involved in certain of these biologic patterns of defense¹⁴⁻¹⁷. Jacobsen¹⁸ and Faulkner¹⁹ have induced experimentally in human subjects spastic contraction of the esophagus during emotional stress and subsequent decrease in the contractile state during relaxation and reassurance. It is the purpose of this investigation to explore further the relationship of life situations and emotions to esophageal functions and, in particular, to cardiospasm.

METHOD

Fourteen subjects were selected at random from a group of patients who complained that swallowed food seemed to stick in the retrosternal region. In each instance, obstruction to the flow of barium into the stomach was demonstrated by x-ray. These patients were compared with 20 asymptomatic control subjects.

A barium mixture was prepared without flavoring, consisting of 142 gm. of barium in 100 cc. of water. The subject was given a "mouthful" of 30 cc. As soon as voluntary swallowing had occurred on command, the time required for (a) the head of the column of barium to enter the stomach and (b) for essentially all of the material to reach the stomach were noted.

The observations were carried out in the standing position. Not uncommonly when cardiospasm was present, the column of barium began to enter the stomach very quickly after it reached the level of the diaphragm, but then was suddenly "pinched off", so that most of the barium remained in the esophagus. The time required for the latter major portion of the swallowed barium to enter the stomach was designated as the "mouth to stomach time".

Each subject was repeatedly examined under a variety of circumstances. On a given day, before any stimulus was applied, at least two "control swallows" were timed. In the study of patients, the stimulus usually consisted of a discussion of emotionally charged life situations.

Most of the patients with cardiospasm were followed from week to week, their swallowing being observed fluoroscopically and special note being made of day to day changes in symptoms, life situation, attitude and emotional state.

OBSERVATIONS

Two types of motility disturbance were noted from fluoroscopic observation. One consisted of frequent irregular contractions of the lower $\frac{2}{3}$ of the esophagus. This type of disturbance has been well described by Templeton²⁰. It was invariably prominent in cardiospasm without marked dilatation of the esophagus, but less marked when the esophagus was greatly dilated and elongated. The character of the movements appeared to be uncoordinated rather than propulsive. As a result, the barium was milked up and down the esophagus. Often



FIG. 1. Effect of diaphragmatic contraction (deep breath) upon esophageal obstruction in a subject with cardiospasm. A. Normal respirator Excursion. B. Deep breath.

a globule of barium appeared to bounce as high as the arch of the aorta and then fall like a water hammer, to be suddenly stopped at or near the diaphragmatic hiatus. The second type of change apparently involved a sustained contraction of the diaphragm, with "pinching off" of the column of barium, with diminution or absence of peristaltic activity in the lower half of the esophagus. This latter was often associated with dyspnea of the "I can't get a full breath" variety, and has been described in another communication²¹. In these subjects and in numerous asymptomatic individuals, temporary esophageal obstruction at the diaphragm could be demonstrated when barium was swallowed during breath-holding in deep inspiration. Nine of the subjects with clinical cardiospasm displayed this phenomenon (Fig. 1).

Comment: Generally speaking, our findings support both the views of Jack-

son²² concerning the diaphragmatic pinchcock and the currently widely held concept that some cases of "cardiospasm" are due to a hypermotility of the lower $\frac{2}{3}$ of the esophagus, commonly designated as "esophagitis". The diminished motility in the presence of wide dilatation of the organ has been explained on the basis of damage through stretching of the neural plexuses by the retained bolus, although Lendrum²³ has considered the neural damage to be beyond that attributable to such stretching. A critical review of the data from various sources and the theories concerning the origin and nature of cardiospasm has been published by Alvarez²⁴.

The variability of esophageal function in relation to problems and conflicts of the day to day situation and its modifiability under experimental circumstances are illustrated in the case records which follow. Ten of the 14 patients are described in more or less detail below.

Hypermotility of esophagus with minimal obstruction and no dilatation: Case 1: Mr. C. H. A 42 year-old minor business executive complained that swallowed food had stuck in the substernal region on occasion for the previous 2 years. For 4-5 years prior to that time, he had noted excessive hiccoughs, often relieved by induced vomiting. 17 years earlier, he had married a woman whom he considered beneath him socially because she had become pregnant as a result of sexual intercourse with him. After marriage, the patient became increasingly stiff, pompous and preoccupied with symbols of respectability. He was particularly sensitive to any real or imagined slur to his dignity or probity. He was wary of being "pushed around", and said "I can't stand it when anyone tries to shove anything down my throat." He had an extraordinary memory for past humiliations, and recounted them in the utmost circumstantial detail. His chief concern at the time he came to the New York Hospital with troublesome complaints of dysphagia was lest his 17 year-old daughter repeat her mother's performance and "disgrace the household". Fluoroscopic and x-ray examination showed the esophagus to be of normal diameter. When he was relatively relaxed and unperturbed, his swallowing time was normal (5 seconds), as shown in Fig. 2. One week later when he was equally contented his swallowing time was again short (7 seconds). He then submitted to an ordinary cold pressor test with a great deal of tension and dramatic stoicism. He perspired profusely, and during the period when his hand was in the ice water, a swallow of barium was retained in the esophagus for 5 minutes. Marked hypermotility was noted. A month later, his swallowing time was 30 seconds on repeated control observations. A discussion was then begun in which the subject of his daughter "fraternizing with somewhat low characters" was dwelt upon. At this point, a swallow of barium was retained in the esophagus for 4 minutes. Later, after strong reassurance, his swallowing time was reduced to 12 seconds. Thereafter, his swallowing time was repeatedly found to be normal (Fig. 2) until following the occasion of his wife's leaving him, when again the barium was retained in his esophagus for longer than 8 minutes. After a therapeutic interview in which possibilities for reconciliation were stressed, the swallowing time shortened again to 10 seconds.

Case 2: Mr. F. L. A 26 year old man had complained of intermittent substernal tightness on swallowing for one year. He was chiefly concerned over sexual inadequacy and failure to consummate his marriage. There was no esophageal dilatation (see Fig. 1). When put at ease, the barium swallow went through in 9 seconds, but when his sexual performance was pessimistically discussed, he developed tightness in his chest, spasm of the lower esophagus, and delay of the passage for more than five minutes.

Hypermotility of esophagus with intermittent prolonged obstruction and minimal dilatation: Case 3: Mr. S. W. A 43 year old Italian baker, had noted almost daily for the previous 3 years a sensation of swallowed food sticking in the lower substernal region. Frequently, the sensation was followed by regurgitation of the swallowed bolus. These symptoms had been noted occasionally since his childhood, but had only

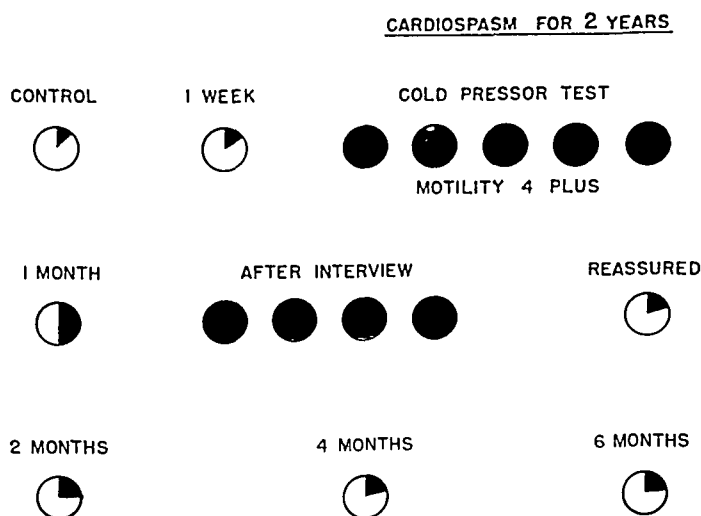


FIG. 2. Diagrammatic representation of delayed passage of barium through the esophagus in a subject with intermittent cardiospasm. Each black circle represents 1 minute, and the black segments are fractions of a minute. (Case 1)

become seriously troublesome 3 years before he was first seen at the New York Hospital.

The patient was born in northern Italy where he lived until he came to this country at the age of 28. His father was a strict, unaffectionate fisherman. Sticking of food in the substernal region had first been noted by the patient when, as a child cooking on a campfire with his friends, he often had to run home in fear of being late and in hopes of escaping his father's wrath. The hot potatoes that he had been cooking over the fire seemed to stick in his gullet.

Later, the patient left his family to come to the United States. Here he worked as a baker, remained unmarried and lived in comparative isolation. He was taciturn at work and rarely expressed his feelings, although he readily felt slighted, humiliated and resentful. He recalled unpleasant incidents in the utmost detail, and he often brooded for months over the implications of some casual word of an associate or seethed repeatedly over the recollection of some fancied slight.

His current troublesome episode of dysphagia had begun after Italy had become

engulfed in the recent world war, in a setting of anxiety concerning his parents, who were still living in Trieste, and guilt over having left them for the comparatively comfortable and secure situation in the United States.

At times of relative relaxation and contentment, this subject displayed no esophageal obstruction, but it was found during day to day observations that significant

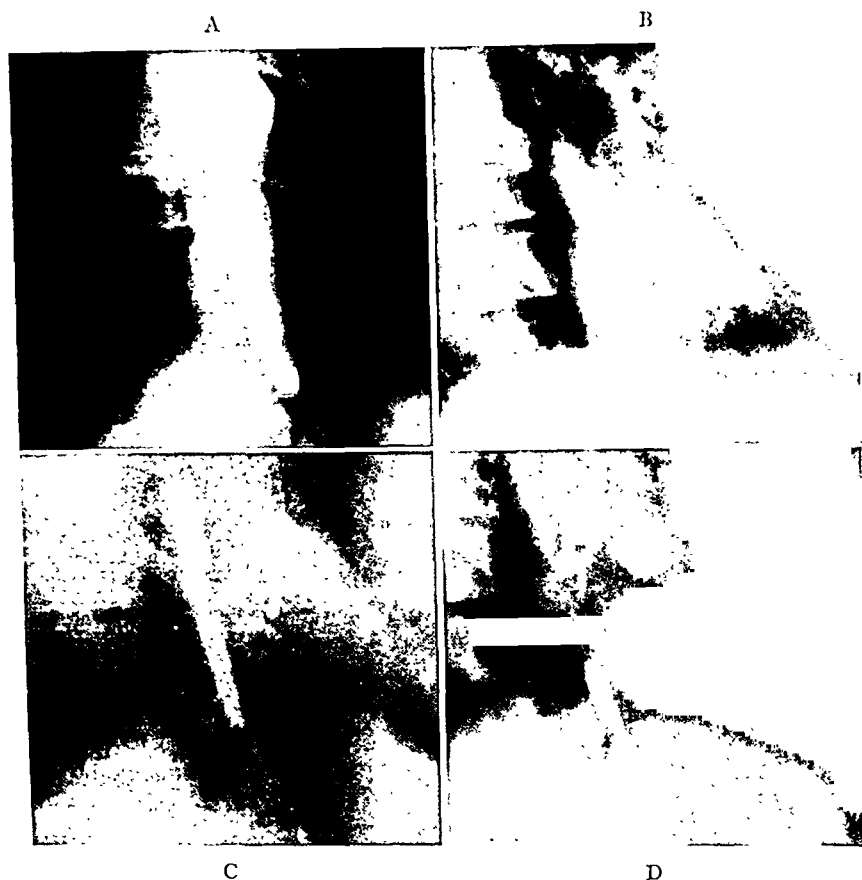


FIG. 3. "Spot-film" X-rays following a single swallow of 30 cc. of barium. A) $7\frac{1}{2}$ min. after swallow on day after dispute with "girl friend." B) $6\frac{1}{2}$ min. after swallow on day following reconciliation. C) and D) $6\frac{1}{2}$ min. and 30 min. respectively after swallow at a time of conflict concerning employment. (Case 3)

delay in the passage of a barium swallow from mouth to stomach occurred in association with the usual symptoms of cardiospasm at times of special conflict as, for example, when a rival baker's union obtained pay increases for their members. In short term experimental situations, it was possible to induce significant esophageal obstructions by bringing up for discussion such sensitive topics as the welfare of his family in Trieste or the employment policies of the New York baking companies and their attitude toward striking employees.

In Fig. 3 are shown "spot film" x-rays taken at varying intervals after 30 cc. of barium had been swallowed. They illustrate the range and variability of esophageal function during relative security on the one hand and conflict on the other. "A" was taken during a period of esophageal obstruction and hypermotility the day after a dispute with his "girl friend" which he was unwilling to discuss. "B" was taken a week later after their differences had been satisfactorily patched up. "She's too good." No cardiospasm was noted. "C" and "D" were taken 6½ and 30 minutes respectively after a barium swallow during the conflict concerning the baker's strike. On this occasion he was especially taciturn and grim. Hypermotility was marked and obstruction was apparent for more than 30 minutes. Not until the following day did he talk freely about his preoccupations. Then he spoke with evident resentment, and said, "We working people should stick together." He said he had been reminded of a personal affront he had sustained in the past, and recounted in the utmost detail an incident of 3 years ago when a minor boss at a bakery refused him a Christmas vacation. "That still makes me mad." On another occasion repeated control swallows were evacuated from the esophagus within 2 minutes. Then a discussion of his parents in Trieste was undertaken in which he caught an implication that he may have deserted them to the Nazis. During this discussion, the barium was delayed 35 minutes in the esophagus. Prompt and vigorous reassurance was then begun, and 10 minutes later a final swallow of barium had completely passed into the stomach within 5 minutes.

Case 4: Mrs. J., a 49 year old widowed Greek schoolteacher, complained of pain in the mid-chest and between the shoulder blades for one year. Whenever she ate at the time the pain was present, food seemed to stick in the midsternal region. There was a good deal of hiccupping, and she occasionally regurgitated a part of her meal. Prior to this time, her general health had been good, except for occasional palpitation and abdominal pain, which led to and was relieved by cholecystectomy for gall stones in 1925.

Born in Constantinople, the patient was the youngest of 5 children. Her father, a factory manager, died during her early childhood. Her mother was a warm but anxious woman who lived to the age of 90. After coming to the United States at the age of 21, the patient was married in 1923 to the editor of a Greek language newspaper. They were happy together, but the husband died 2 years after their marriage shortly before the delivery of her second child and first son. The baby died at 2 months of pneumonia. In 1927, mainly because of the pressure of poverty, she married a cruel Greek delicatessen owner. The latter deserted her while they were visiting in Greece, taking their only child, a 9 day old son, with him. The patient eventually managed to return to the United States, but the husband refused to send their son to her.

Following an episode in which the patient accidentally dropped a suitcase on her daughter's abdomen, the latter began to complain of constipation, and she eventually died of an intestinal carcinoma. The patient reacted with profound depression to her daughter's death. She considered her her only link with her first husband, and 6 years following the death was still continually kissing the girl's photograph and weep-

ing by the hour. At the end of the recent World War, the patient received news of her son, and managed with the help of the Red Cross to have him brought to the United States to live with her. Her husband had been mayor of a Greek town at the time of the Italian invasion, and had escaped to an unknown whereabouts. When her son came to live with her, she found that he resembled in many respects her second husband. He was bright, tense, restless and undemonstrative. Her chest pain and dysphagia began shortly after the son moved in with her.

Fluoroscopic examination revealed the esophagus to be only slightly, if at all, dilated, but motor activity was markedly increased and the swallowed barium was squeezed up and down in the organ before it gained access to the stomach (Fig. 4). On the occasion of the first examination prior to interview, essentially all of the barium was emptied from the esophagus within 5 minutes. Following the recital of the events described above, however, she appeared tearful, tense and dejected, and re-

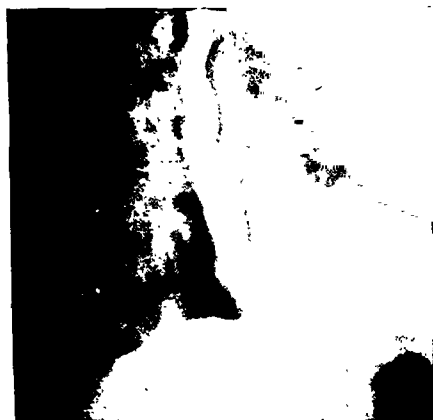


FIG. 4. Absence of significant dilatation of esophagus in a subject with long standing but intermittent symptoms of cardiospasm. (Case 4). X-ray taken 5 min. after barium.

peatedly it took approximately 30 minutes for a swallow of barium to be completely evacuated from the esophagus. When she was reexamined a week later, she seemed even more dejected and taciturn. She said that she couldn't get her mind off her daughter. When, after 17 minutes, at least 50 per cent of the swallowed barium remained in the esophagus, she was given 0.2 gm. Sodium Amytal in a 10 per cent solution intravenously, in an attempt to induce relaxation and diversion. She resisted vigorous attempts at reassurance, and only became more depressed and fixed on her conflicts concerning her children. While the barium continued to be held within the esophagus she said, "I want to die. I don't like this world. I want to see my daughter. . . . Boys don't respect their mother. . . . My daughter was different. . . . I don't want to wake up". When the experimental observation was concluded 37 minutes after the barium had been swallowed, at least 20 per cent still remained in the esophagus. 2½ months later, when the patient was more relaxed and cheerful, the esophagus nearly emptied in 6 minutes.

Sustained Obstruction with Moderate Dilatation of Esophagus and Moderate Hypermotility: Case 5: The patient, R. D., was a 52 year old housewife who complained of painful sticking of swallowed food in the retrosternal region, intermittently for the previous 7 years but seriously troublesome for only the past 8 months.

She had had, since her mother's death 35 years before, numerous complaints including constipation, nausea, vomiting and epigastric pain. Five abdominal operations were done; appendectomy in 1913, exploratory laparotomy in 1914, subtotal hysterectomy in 1938 and later a bilateral oophorectomy, but despite these procedures her symptoms remained unmodified. Diagnostic and therapeutic efforts did not become focussed on the esophagus until dysphagia assumed prominence among her complaints.

The patient was born in Pinsk, Russia, and came to this country with her mother at the age of 14. Her father, a kitchenware importer, had died accidentally at 34, but her mother lived to 56 working as a cook and died suddenly of heart disease when the patient was 16. There were 6 brothers and sisters who ranged from 7 to 19 years older than the patient. She had little contact with her brothers and sisters. One brother was killed in World War I and the other died of a complication following a throat infection at 24. She identified herself chiefly with her mother, a meticulous, hard working woman, somewhat grim and lugubrious, who wept at any mention of her dead husband. The patient was her mother's favorite and lived alone with her from the age of 9 until the latter's death. She feels that she learned from her mother to suppress her feelings and to get on with people by being submissive. She was easily humiliated by apparently trivial incidents and often ruminated for days over her problems.

Obesity, varicose veins and the operative scars on the abdomen were the only notable findings on physical examination. X-rays revealed diverticulosis of the sigmoid.

The earliest x-ray study of the barium-filled esophagus revealed evidence of obstruction near the level of the diaphragm with moderate dilatation above.

Considerable variability in the diameter of the esophagus gave evidence that hypermotility was associated with the obstruction. At the time of the experimental observation, her esophageal disturbance was minimal and the swallowing time was repeatedly less than 15 seconds. When suddenly reminded of a domestic conflict, however, the length of time required for a swallow of barium to pass from hypopharynx to stomach was lengthened to 30 minutes. Following reassurance, the esophageal obstruction was relieved and the swallowing time was again 15 seconds. Surgical esophagogastrostomy was performed September 1947. Following operation the esophagus emptied promptly but pain in the substernal region persisted on occasion and she suffered an intensification of her complaint of nausea.

Case 6: R. S., a 57 year old Jewish housewife, born in Galicia, came to the United States at age 25. For 5 years she had noted the sensation of swallowed food sticking in the substernal region. This was associated with excessive belching and pain which could be relieved by regurgitation.

Her father, who died at 67, had been a tense, rigid man, subject to bouts of diarrhea. Her mother apparently had Raynaud's disease.

The patient was the eldest of 4 girls and a boy. Her childhood in Europe was recalled as an unhappy one because of her parents' cold, unaffectionate nature. She early learned to suppress her feelings and sought approval by being "good". During early adolescence she began to be handicapped by progressive myopia and displayed the cold, blue hands of Raynaud's disease. She became increasingly sensitive concerning these disabilities and, though she never showed her feelings, she would brood and weep in solitude for days over the most casual slight. Her only warm attachment was to a younger sister who died in 1937 of tuberculosis.

She had 12 years of schooling in Europe and was married at 23 to a man whom she considered "unclean" and with whom she was never happy. She divorced him before coming to the United States.

In this country she married a man 20 years older than herself, ("I was never attracted to him, I loved him like a father"). Her symptoms of esophageal obstruction began in a setting of extreme sexual frustration and conflict. While her aging husband made more and more vigorous sexual demands on her he became increasingly impotent. He continually aroused her almost to the point of orgasm, but he was never able to achieve an erection to consummate the episode. The patient resorted to clandestine masturbation. She felt a great deal of guilt over this as well as dejection, humiliation and resentment against her husband. She became more and more seclusive and preoccupied with her physical deformities. "I have been denied everything. I haven't had a happy day in my life".

Abnormalities noted on physical examination included hypertension (B.P. 154/96), convergent strabismus, bilateral nuclear cataracts, advanced myopia, atrophy and scarring of the terminal phalanges of hands, emphysema and obesity.

X-rays revealed marked dilatation and slight elongation of the esophagus with a variable degree of obstruction. (Fig. 5.)

At the first 3 experimental sessions evacuation of a single swallow of barium from the esophagus required approximately one hour (Fig. 6). She was dejected and tearful and could not be distracted from her morbid preoccupations with her "tragic lot". Accordingly, she was admitted to the hospital. She was greatly relieved and pleased to be afforded a respite from her husband's continual sexual stimulation and promptly her swallowing time shortened to 5 minutes. She was cheerful, relaxed and free of symptoms. Two days later the swallowing time was observed to be 5 minutes again. On this occasion, after she was reminded of the need to return to her husband upon ultimately leaving the hospital, she became tense, wept briefly and a fresh swallow of barium was delayed in the esophagus for 15 minutes. Following this observation she was quickly reassured and encouraged and then again asked to swallow barium. This time the opaque material was emptied into the stomach within 3 minutes. When she came to the laboratory the following day, however, the patient was tense and dejected. After much hesitation she tearfully confessed her inability to give up masturbation. Vigorous efforts at reassurance apparently had little effect on her. Her preoccupation with her own guilt soon became diluted with feelings of resentment, humiliation and frustration which arose out of interpersonal conflict with the other patient in her room. She considered the latter's attitude to be haughty and insulting. She was unable to sleep because her companion made a noisy disturbance at night and

always had her own way with the nurses in the matter of whether the window should be up or down. On 3 successive fluoroscopic observations extending over 4 days the barium was retained in the esophagus for more than an hour, more than half an

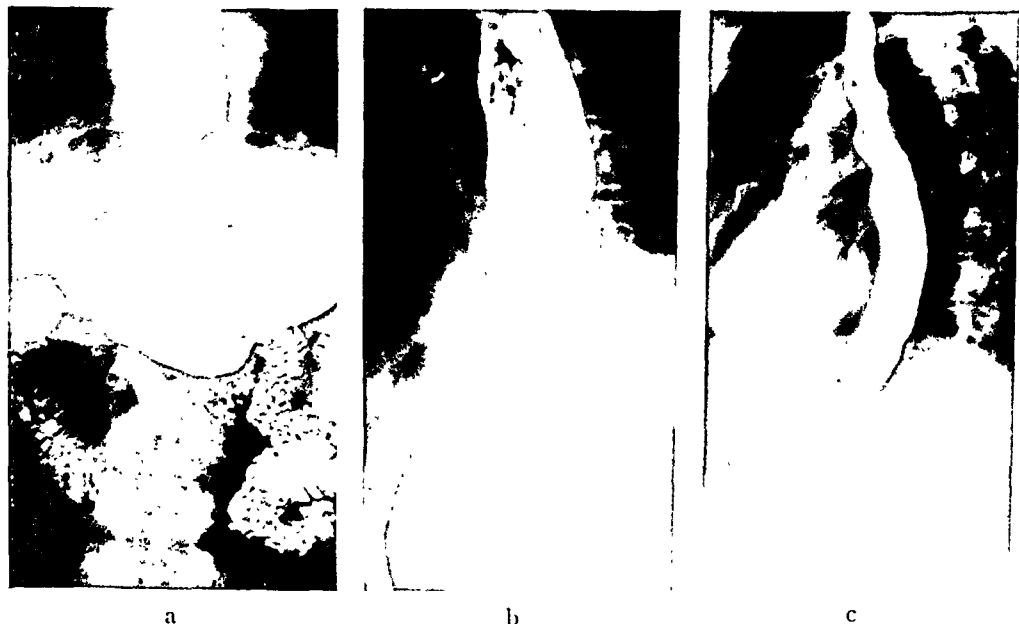


FIG. 5. Cardiospasm for 5 years. a) x-ray at time of admission to hospital; b) 3 weeks later—film taken during quiet breathing; c) same day—obstruction at level of diaphragm during full inspiration. (Case 6)

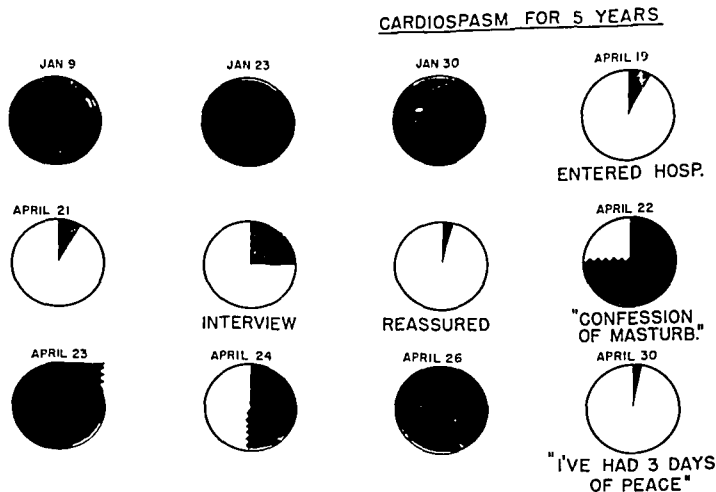


FIG. 6. Diagrammatic representation of variability of esophageal function from day to day and during several experimental observations. Each black circle represents 1 hour. (Case 6)

hour and approximately an hour. Finally, much to her relief, she was moved to a single room. When examined 3 days later she appeared relatively relaxed and cheerful. Her swallowing time was only 3 minutes and she averred, "I have had 3 days of peace". (Fig. 6.)

Comment: Although the esophageal obstruction in this individual was markedly variable and corresponded closely to her life situation, attitudes and mood at the time, motor activity in the esophagus was never pronounced, being less than described in the patient R. D. above.

Sustained Obstruction with Marked Dilatation and Elongation of Esophagus and Little Evidence of Hypermotility: Case 7: Mr. G. F. was a 37 year old married accountant who had noted over the past 10 years frequent sensations of food sticking in the retrosternal region associated with pain and often relieved by regurgitation.

He was born in New York City, the oldest of 4 children of German Jewish immigrants. His father was a restrained and mild mannered tailor who avoided responsibility and toward whom the patient was aware of feeling some contempt. His mother was an unaffectionate, somewhat domineering woman, ("I don't ever remember kissing my mother"). She was extremely ambitious for social and financial success for the patient and withheld from him approval and support whenever he failed to excel. The patient was a feeding problem in infancy and childhood and was forced to eat by his mother. He also displayed temper tantrums from early childhood and bit his nails. He recalled feeling intense resentment for a sister whom he considered favored by his mother. Under pressure from the family he graduated from college with honors in 1933. He failed his first examinations for C.P.A., however, and it was at this time that his dysphagia began. Two years later he left home in protest against his parents' authoritarian attitude. In 1939 he married, with full approval of both families, a girl 16 years older than himself. Their adjustment was generally good from the beginning. The patient was at first apprehensive concerning his ability to finance a family but yielded to his wife's pressure to have children. At the time he was seen by the authors, he had a son, six, and a daughter, four. Both he and his wife were aware that they favored the girl. ("The son is unfortunately like me but I try to like him").

The patient was inclined to harbor grudges for long periods of time, to brood over frustrating or humiliating episodes. Often he recalled unpleasant events in much greater detail than did those with whom he shared them. He, himself, had noted the close correlation between his dysphagia and his situation and emotional state. His worst attacks had occurred at times of frustration in his work or home life, as, for example, when out of a sense of duty he entertained his sister and her husband at dinner and they arrived at his house late without apology or explanation; or when it was necessary for him and his wife to sleep in the living room in order to accommodate his recently widowed father-in-law. He was usually free of symptoms when on holiday.

Examination of the patient revealed no striking findings. He was a small, slender man but not at all emaciated, appearing about his stated age.

X-rays of the esophagus showed the organ to be greatly dilated, elongated and tortuous. (Fig. 7.)

On the first 4 occasions on which he was observed experimentally moderate hypermotility of the lower end was noted. The barium swallow remained within the esophagus throughout the period of observation. He was tense, dejected, occasionally tearful and deeply preoccupied with guilt concerning his relationship to his children. His anxiety was accentuated by his daughter's having a severe bout of

asthma. As her condition cleared up and as the patient, under treatment, began to resolve some of his own conflicts, his home situation improved and with it his dysphagia disappeared. ("I am happier because I feel much more warmly toward



FIG. 7. Markedly dilated and tortuous esophagus in a patient with advanced cardiospasm. (Case 7)

MR. S

CARDIOSPASM FOR 10 YEARS

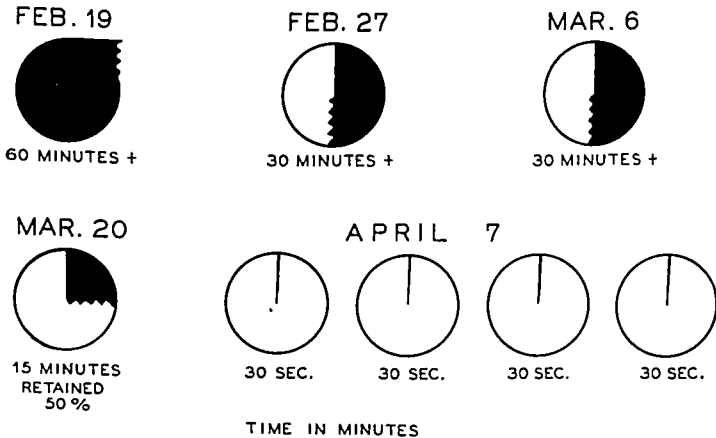


FIG. 8. Diagrammatic representation of variability day to day and during several experimental observations. Each black circle represents an hour. Note relatively normal emptying of the esophagus on occasion, despite advanced deformity. (Case 7)

my son now"). Four successive swallows of barium were cleared through the esophagus within 30 seconds despite its elongation and tortuosity. (Fig. 8).

Case 8: C. L., a 50 year old white American housewife, had noted the sensation that swallowed food stuck in the retrosternal area off and on for 20 years. Attacks occurred at periods of tension, as when extra people were suddenly brought home for dinner. The condition had been seriously troublesome for 2 years, and since then had been

associated with attacks of severe dyspnea, cough and wheezing, relieved by injections of epinephrin.

The patient came from an Early American background. Both parents were stiff, puritanical individuals. Up until her death, which followed a cholecystectomy at the age of 68, her mother complained of dysphagia similar to the patient's. It was during her mother's terminal illness that the patient's dysphagic symptoms began. The patient had always been greatly concerned with the approval of those about her, and in particular her mother. She felt that her own domestic responsibilities had kept her from adequately caring for her mother's needs. She was, generally speaking, timid and perfectionistic, readily moved to tears and anxious in the face of unpredictables. X-ray and fluoroscopic study during a not very troublesome period revealed the esophagus to be hugely dilated and tortuous. There was no obstruction to the flow of barium, however, although the material puddled and remained in the lowest loop of the sigmoid deformity of the esophagus. After 3 swallows of barium were observed to enter unobstructed into the stomach, the patient was told her condition required a surgical operation. She immediately became tense, tremulous and tearful, and flatly refused the suggestion. She was promptly given a fresh swallow of barium. This time complete obstruction was noted at the level of the diaphragm. There was no evident motor activity in the esophagus, but the barium was retained for more than $1\frac{1}{2}$ hours.

Stages of Esophageal Changes in Cardiospasm and their Reversibility

If it were true, as suggested above, that the natural history of cardiospasm includes a continuum starting with hypermotility and increased contractile state of the esophagus, followed by the dilatation inevitably associated with obstruction and ultimately ending as an elongated, stretched and atonic organ, one should be able to identify such changes in patients followed over the years. Opportunity to check the validity of this proposition was available from earlier records and x-rays of subjects in our series. In only one case of cardiospasm were x-rays available from the time of onset of obstructive symptoms. The series of films appears to support the postulate that hypermotility and generalized constriction precede the stage of dilatation and atony in the esophagus (Fig. 9).

Case 9: The patient, T. K., a 33 year old housewife, had noted a feeling of sub-sternal pressure immediately after swallowing for 3 years. Excessive hiccupping occurred for several days at the time of onset. X-rays taken within a few weeks showed hypermotility of the esophagus which was labelled esophagitis (Fig. 9A). Three years later, the characteristic esophageal dilatation of cardiospasm was evident (Fig. 9B). Following surgical esophagogastrostomy, the esophagus resumed its original non-dilated appearance.

Gill and Child²⁵ have reported effective reduction in the lumen of the esophagus by a surgical esophagogastrostomy even in subjects with relatively advanced dilatation.

Under suitable circumstances, even without operation, it was apparently possible for the morbid chain of events referred to above to be interrupted and the process reversed, with reversion of a moderately dilated esophagus to one with a normal diameter.

Case 10. The patient, K. C., a 40 year old housewife, had begun 7 years before to have substernal sticking sensations and the regurgitation of food after almost every meal. During this time she had lost 16 pounds.

The patient had been born in Poland, the second child of five of a small retail merchant. She was separated from her father from ages 4 to 12, because of the war. Both parents, especially the father, were humorless, unaffectionate people. The patient was dominated by her older sister, with whom she had many disputes concerning household duties, such as washing the dishes. The sister always won these arguments because the patient was unwilling to press her point. At times when her



FIG. 9A. "Esophagitis". Undilated but partly obstructed esophagus a few weeks after onset of symptoms of cardiospasm. (Case 9)

FIG. 9B. The same patient three years later, showing typical findings of cardiospasm with moderate dilatation of the esophagus prior to operation.

sister, with whom she slept, wet the bed, the patient would be forced to change places and lie in the wet portion. Instead of retaliating against such acts of aggression, the patient learned to get along with people by being submissive. At age 18, she married a milliner, and by him had two daughters. Both manifested frequent anorexia and vomiting in infancy.

The onset of regurgitation had followed an emergency appendectomy performed on her eldest daughter. The patient felt that she was responsible for delaying this necessary procedure. Later, her older sister was hospitalized with her third pregnancy, complicated by pneumonia. For this reason, the sister's two children were left with the patient. At the same time, a younger sister had broken her leg in an automobile accident and the patient's husband had lost his job. She reacted to these problems both by working and by weeping, but not by complaining to others. When her older sister finally returned home, the patient, exhausted, quickly returned the sister's children to her. Instead of being thanked by the sister and her husband, she was denounced

for not having kept the children longer, during the sister's convalescence. At this, she said she was overwhelmed, and felt alone and frustrated in her desire to help others. For some time thereafter, she vigorously devoted herself to serving others in order to satisfy her conscience, but she nevertheless felt depressed, and brooded over the fact that she was rewarded neither by money nor by gratitude.

Physical examination revealed no significant abnormalities. X-rays of the esophagus showed typical cardiospasm with moderate dilatation of the esophagus (Fig. 10A).

She was treated by various medical measures over a period of $2\frac{1}{2}$ years. Dilatations of the esophagus gave partial relief for one day each, and with this slight improvement the patient went to work. She became less preoccupied with her older sister's ingratitude and felt less compelled to do good to others in order to satisfy her conscience. With this change in attitude, there was profound improvement in her esophageal function. Regurgitation occurred only rarely; the substernal sticking sensations be-



10A

10B

FIG. 10A. Marked dilatation of esophagus 7 years after onset of symptoms of cardiospasm.

FIG. 10B. The same esophagus 6 years later, after partial subsidence of symptoms. (Case 10)

came intermittent, milder, and could be relieved by drinking water. She regained her lost weight. Exacerbations of symptoms could now be exactly correlated with periods of stress, as when her newlywed daughter's husband left her.

During 1948, film and fluoroscopic examination of the esophagus showed no dilatation of the organ. There were, on the other hand, vigorous, uncoordinated, sometimes retrograde contractile waves traversing the esophagus from the arch of the aorta to the diaphragm (Fig. 10 B).

Other subjects: Four other subjects with cardiospasm not described here in detail were similarly studied. Clinically, all 4 fell into the category designated above as "moderate dilatation of the esophagus, etc.". In all of them, it was possible to correlate episodes of symptomatic exacerbation and remission with variations in life situations, feeling state and attitude. Also, in the short term experimental situation variability in the degree of esophageal obstruction was demonstrated in association with changes in the emotional state.

Epitome of the personality of the patient with cardiospasm

It will be evident from the brief description of each subject that from the characterologic point of view, certain attitudes and traits are common to those with cardiospasm. As a group, they are dour, humorless, wary, suspicious, non-committal and defensive rather than aggressive in their dealings with day to day problems. Moreover, they are given to suppressing rather than expressing their conflicts and feelings. They are circumstantial, bear grudges and brood unusually over minor slights and humiliations. In short, in their attitudes and behavior, they are ruminative, and rumination is suggested by their esophageal dysfunction.

Cardiospasm as a protective reaction to noxious stimulation

In view of the consistently observed relationship between stressful situations and the occurrence of obstructive esophageal changes, the possibility suggested itself that this change might occur as part of a defensive reaction of the organism, appropriately following the ingestion of noxious agents, but less helpful in dealing with frustrations and humiliations encountered in day to day living. In an effort to elucidate this question, healthy persons were subjected to a graded series of noxious stimuli, first directed at the gastro-intestinal tract, then generally at the integrity of the organism. Finally, the subjects were exposed to noxious stimuli of a symbolic nature.

A healthy 23 year-old female was repeatedly observed fluoroscopically during swallowing. Under ordinary circumstances, the swallow of barium was completely evacuated from the esophagus in 8 seconds or less. Accordingly, a mixture of barium which was thinner than usual was prepared so that after chilling it had approximately the same consistency as the mixture usually used at room temperature. Upon swallowing the mixture at 6.5 degrees C., she noted an uncomfortable sensation of cold in the retrosternal region. The barium began to enter the stomach within 2 seconds, but complete emptying of the esophagus was delayed until 7 seconds. Marked increase in motor activity in the esophagus was noted. She was promptly given a second swallow. This one began to enter the stomach in 3 seconds, but complete passage was delayed until 50 seconds. Throughout the interval, vigorous contractile activity was noted, with irregular constrictions of the lower half of the esophagus which milked the barium back as high as the arch of the aorta. By this time, the cold sensation was moderately distressing. Following a third swallow, a substernal tension of tightness was noted. Most of the barium remained in the esophagus for more than 2 minutes, and the phenomenon of "pinching off" with each descent of the diaphragm was noted. In addition to this, the contractile activity of the lower $\frac{2}{3}$ of the organ was more marked than ever. Fig. 11A is a spot film taken 2 minutes after swallowing. After 30 minutes rest, the subject was given a series of three swal-

lows of hot barium at 63 degrees C. With each swallow there occurred a sensation of burning in the esophagus, and marked increase of motor activity was noted. The esophagus was emptied in 12 seconds after the first, 25 after the second, and after the third, the barium remained for more than one minute. Fig. 11B is a spot film taken at one minute. Finally, after another rest of one half-hour, the subject swallowed the standard barium mixture, to which had been added approximately 20 drops of tabasco sauce. A painful sensation of burning accompanied each of 4 swallows and persisted for several minutes thereafter. The esophagus emptied in 44 seconds after the first, 46 after the second, 25 after the third and one minute after the fourth. Following this fourth swallow, she noted dyspnea with difficulty in getting a full breath, and "pinching off" of the barium at the diaphragmatic level was quite plain.



11A



11B

FIG. 11A. Transitory evidence of cardiospasm in a normal subject following ingestion of extremely cold barium.

FIG. 11B. Transitory evidence of cardiospasm in a normal subject following ingestion of extremely hot barium.

Comment: The fact that cardiospasm could be provoked by the application of such noxious stimuli to the esophagus was first demonstrated by Kronecker and Meltzer²⁶ and later by Von Miculicz²⁷.

Transitory cardiospasm in normal subjects following general threats to the organism.

The biologic pattern of esophageal constriction is altogether appropriate as a defense against ingested irritants. In order to determine whether or not such a reaction might be invoked, perhaps less appropriately, under other circumstances, 20 healthy persons were subjected to a variety of stresses while their esophagi were observed fluoroscopically. While under neutral conditions, the swallowing time of all these subjects was twelve seconds or less.

Fourteen individuals were exposed to pain induced by immersion of the hand in ice water. Only three of these appeared to be significantly distressed by this

experience. These three displayed an increase in their swallowing time to 25 seconds or longer. In 11 subjects, much more prolonged and distressing pain was produced by compression of the head with a metal device equipped with 18 constricting screws. Four of these subjects were aware of a significantly troublesome conflict between desire for self-preservation and desire to appear as brave as their fellows. These four showed delay in the passage of barium through the esophagus from 42 to 102 seconds. Two subjects failed to react with esophageal

TABLE I
Symptoms and signs observed during experimental stress (headscrew) in eleven subjects

Weakness.....	8	Cardiospasm.....	4
Giddiness.....	6	Nausea.....	7
		Vomiting.....	1
Diastolic hypertension.....	7	Sighing.....	7
Bradycardia.....	1	Yawning.....	3
		Latent Tetany.....	3
Sweating.....	10		
Flushing of skin.....	8		
Seborrhea.....	6	Photophobia.....	4
Pallor, cold skin.....	5	Lacrimation.....	2

MR. W.

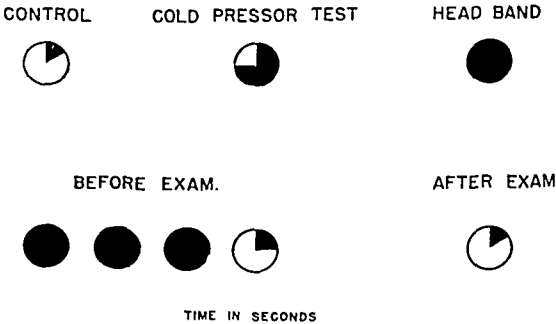


FIG. 12. Normal subject in whom a symbolic threat was more effective than pain in producing esophageal constriction.

constriction to the cold water, but required 45 and 60 seconds respectively to evacuate the esophagus during headache.

The other symptoms and signs displayed by the subjects during this formidable experience are listed in Table 1. They indicate that the reaction to stress was a generalized one. Sweating, sighing, nausea, and diastolic hypertension were especially frequent. In three individuals, hyperventilation was severe enough to produce latent tetany, manifested by positive Chvostek and Trousseau signs. Five students who had undergone both the ice water and the head-screw experiments were fluoroscoped almost daily for two weeks. At the end of

this period, they were due to take important oral examinations. In the first week, their "mouth to stomach" times were less than 12 seconds in all instances. Just before the examinations, two of the group who had not been affected by the cold pain or by the headscrew had swallowing times prolonged to nearly 2 and over 3 minutes respectively. They felt that the chance of failing was a greater threat to their security than were the earlier painful stimuli. A third subject reacted to all three stimuli by partial esophageal occlusion. He emptied his esophagus in 10 seconds when relaxed. When his hand was in ice water, he required 45 seconds, and with the headscrew, 60 seconds. Before his oral examination he took three minutes and a quarter. Throughout this period, marked hypermotility of the lower half of the esophagus was noted. After the examinations, his esophagus again functioned normally (Fig. 12).

DISCUSSION

These data and the studies of others indicate that the dilated, elongated, and obstructed esophagus of cardiospasm may be the end state of a process which in its early stages is reversible, and which is never entirely static. Two mechanisms appear to participate in this process. The principal one includes irregular contractile activity of the lower $\frac{2}{3}$ of the esophagus which fails smoothly to propel the bolus and often leads to regurgitation. The second mechanism involves localized obstruction just above the cardia due presumably to forceful contraction of the diaphragm and reduced activity in the lower half of the esophagus. Both of these mechanisms were observed in this study, not only in patients with cardiospasm but also in healthy persons under stress. In general, the esophageal hypermotility and dysrhythmia has been more prominent in early cases, and in those whose esophageal obstruction is milder and more variable. The observations indicate that one mechanism may supplant the other in the evolution of the disorder in an individual patient. Our data suggest that the "entity" often designated as "diffuse spasm of the esophagus" or "esophagitis" may represent an early or mild phase of the "entity" of "cardiospasm" or "megaesophagus".

It would appear that the phenomena of cardiospasm occur as part of a biologic pattern of defense, which is appropriate when used against ingested irritants, but which is also used, less appropriately, by certain persons in their adaptation to more general stresses or threats to the security of the organism. When this pattern is involved continuously or for long periods, as it is in certain "ruminative" individuals, there is evidence that it may lead to the symptoms of dysphagia and ultimately to the structural deformities of cardiospasm.

It is of special interest that the behavior of the esophagus and the degree of obstruction, even in the presence of advanced structural change, may be modified predictably during variations in attitude and emotional state. This strongly

supports the suggestion that these patients may profit by therapy directed at improving the personality adjustment. The occurrence of spontaneous improvement in a patient with a greatly dilated esophagus (Case 10) leads us to suggest that the decision whether to treat the person as well as his esophagus should be based not upon the anatomical and functional state of the esophagus, but upon a thorough appraisal of the possibilities for improvement in the life situation or in the patient's adjustment.

SUMMARY AND CONCLUSIONS

Repeated fluoroscopic observations of swallowed barium sulfate were made on 14 patients with well-established cardiospasm. It was found that the esophageal obstruction of cardiospasm was often associated with marked hypermotility of the lower $\frac{2}{3}$ of the esophagus. Irregular contractile activity was noted even in the presence of moderate dilatation of the organ. Only when the esophagus was widely dilated and greatly elongated was the motility absent. The degree of esophageal obstruction in 9 of 14 subjects with cardiospasm could also be intensified by increase in the contractile state of the diaphragm, as in a deep breath.

Exacerbations or remission of symptoms in these subjects could be correlated with periods in their lives of stress, on the one hand, or relative security on the other. Moreover, in short term experimental observations, it was noted that a discussion of emotionally charged topics was associated with hypermotility and obstruction in the esophagus, while relative security and relaxation were associated with diminution or disappearance of the phenomena of cardiospasm. In a normal subject, the esophageal changes of cardiospasm were induced by the application of local noxious stimuli in the form of heat, cold, and a chemical irritant. Among other normal subjects, a few reacted with cardiospasm to general threats and stresses, including symbolic ones. These data lead to the inference that cardiospasm may occur as part of a biologic reaction to stress, functional and reversible in its early stages.

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A SIMPLE EXPLANATION FOR CARDIOSPASM AND HIRSCHSPRUNG'S DISEASE

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One of the curious features about spasm in two places in the digestive tract is that there can be a marked blockage of the food or its residues without any macroscopic sign that anything locally is wrong. I am speaking of cardiospasm and the narrowing at the distal end of a Hirschsprung's colon. In these places there is no local hypertrophy of the muscle such as one would expect if there had been conflict of one segment with others orad to it.

There are rare cases, also, in which this sort of thing is found in the jejunum. I remember a girl who had to be operated on for a subacute intestinal obstruction. The surgeon found at the lower end of the dilated segment a contracted "napkin ring" of what looked like normal bowel. When this was short circuited, the girl got over the obstruction. A similar case of obstruction in the ileum was reported by Perrot and Danon with a histologic demonstration of injury to the myenteric plexus (see Whitehouse and Kernohan¹). Another case of dilated small bowel resembling a megacolon and without obvious obstruction was seen by Dr. M. A. Spellberg of Chicago.

A SIMPLE EXPLANATION

The literature is full of complicated and highly theoretic explanations for this sort of behavior of the cardia and bowel but, curiously, in the last twenty-seven years, few of the writers on this subject have ever mentioned the extremely simple explanation of the phenomenon which I offered in 1922. Perhaps then it seemed so simple as to be preposterous! Also, because the note was buried in a book, few clinicians ever saw it.

What happened some thirty-five years ago was that while reading everything I could find on smooth types of muscle, I found that in lower forms of life, such muscle, if separated from its nearest ganglion cells, usually contracted down and stayed contracted. This can be seen beautifully in a slug, as shown in figure 1 taken from Biedermann².

An important feature of this explanation is that one does not have to drag in any complicated theory about autonomic nerves centrad to the ganglions in Auerbach's plexus, and one does not have to spin theories about an antagonism between the sympathetic and the parasympathetic nerves. All one has to do to explain the spasm is to demonstrate destruction of those ganglion cells which are in immediate connection with the muscle.

A possible objection to this idea is that in view of some observations I once

made on the bowel of rabbits, one must wonder how a contracted ring of muscle could so thoroughly obstruct the bowel orad to it. What I showed in rabbits was that if one divides the small bowel and restores continuity with a short piece of glass or rubber tubing, the rush waves go through the inert segment, and on reaching the bowel beyond, the intestinal contents stimulate it and start up a new wave (Alvarez, 1924)³. For some as yet unknown reason, the segment of

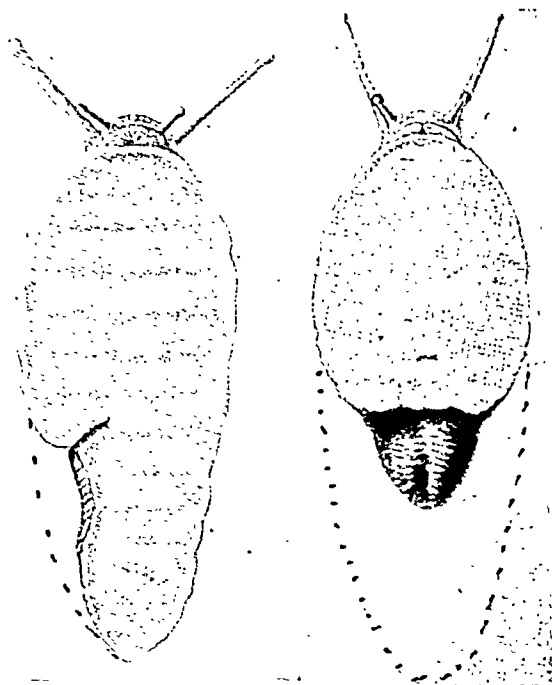


FIG. 1. To show how the nerves function to keep muscle from contracting into a knot: *a*, *Helix pomatia* after denervation of the right rear quarter of the foot, *b*, *Helix pomatia* after denervation of the rear half of the foot. The dotted line shows the appearance of the animal before section of the nerves (from Biedermann²).

bowel without ganglion cells seems to block peristalsis much more efficiently than if it were dead and inert.

CONFIRMATION OF THE SUGGESTION

After discovering the peculiarity of smooth muscle in articles by Bayliss and Starling⁴, Magnus⁵, Jordan⁶, Biedermann² and others, and glimpsing what it could mean in explaining cardiospasm and Hirschsprung's disease, I started searching through the literature, and in the second edition of my *Mechanics of the Digestive Tract*⁷ I was able to report Dalla Valle's⁸ finding of an absence of the myenteric plexus in the unyielding segment at the distal end of the dilated

out any difficulty. In this way they feed their young. I have reported the cases of men who apparently were born without a cardia, and who suffered much because of this lack.³⁰ One such man often has to sleep in a chair because if he lies down, gastric juice may run out of his nose. In his case examination with roentgen rays and the esophagoscope showed no sign of a constriction where the cardia should be. This man, probably, has a throwback to some of his avian ancestors.



FIG. 2. The sharp change at the cardia of man from the esophageal to the gastric mucosa.

THE SUGGESTION THAT THE CARDIA IS AT THE HIATUS IN THE DIAPHRAGM

Several writers have suggested that the cardiac valve is really situated at the hiatus of the diaphragm and that its closure is due to a pinchcock action of the diaphragmatic muscle. Most of the evidence is against this. Some of the best evidence against it is that obtained by the English surgeon, Mr. Rodney Maingot,³¹ who, in many cases, has done a Ramstedt type of operation on patients with cardiospasm. He just slit the muscle of the lower part of the esophagus and the cardia, and in all but 2 of his patients got a fine result. Since he did not do anything to loosen up the diaphragm this shows it had nothing to do with producing the shut-off.

THE RIGIDITY OF THE CARDIA IN CASES OF CARDIOSPASM

From the point of view of a physiologist or a pathologist trying to explain cardiospasm, one of the big puzzles is why the ring of tissue at the cardia becomes so firmly contracted that, in order to open it up, one has to use considerable force in dilating it. One would think that in order to get such a rigid ring, either the muscle would have to hypertrophy greatly, or else much connective tissue would have to form. But, actually, neither of these changes is ever found. The cardia from a patient with cardiospasm looks to the pathologist like that from a normal person. One can easily stick one's finger through the opening, which indicates that the trouble is not so much spasm as an inability of waves to pass. This observation caused Hurst to coin the word "achalasia".

Puzzling also is the fact that a cardia can function so perfectly again after it has been dilated. One would expect it to remain open so that gastric juice would be strangling the patient at night, but it does not.

PSYCHIC INFLUENCES IN THE PRODUCTION OF CARDIOSPASM

There can be no doubt that in many cases of cardiospasm, psychic disturbances have an influence, but in most cases it seems equally obvious that they cannot cause all of the trouble. It is hard to understand how they could produce the sort of firm contraction which needs dilation. One can see how it might produce this after several years, but in some cases one gets a history of only a short period of malfunction. Thus, recently, I saw a stout, sensible, cheery man, who suddenly, two weeks before, had found himself unable to swallow. So far as I could find, there had been no psychic upset, and he did not seem to be either nervous or worrisome or psychopathic. But his cardia was already so firmly contracted that it had to be forcibly dilated.

Perhaps in many cases psychic influences can precipitate spasm in a cardia that has long been undergoing pathologic changes. To illustrate: a refugee physician came one day to say that cardiospasm had just developed. I asked him if he had recently received bad news from Poland, and he said, yes, that just before the spasm came he had been shocked at hearing that his mother and sister had been brutally misused by the Nazis. It seemed to be a perfect case for the psychiatrist, but roentgenologic examination showed a large carcinoma at the cardia! I have seen several such instances.

THE LOGICAL TREATMENT FOR MEGACOLON

It would seem that when a megacolon terminates in a ring of nonconducting muscle the logical treatment would be for a surgeon to remove the ring. Unfortunately, Dr. Claude Dixon tells me that in only about half the cases he has studied was there such a ring. In the other half, the dilatation extended pretty

much to the anus. He and Dr. B. Marden Black have tried removing only this blocking segment but without success. Now Dr. Orvar Swenson³ with Drs. E. B. D. Neuhauser and L. K. Pickett have performed the operation of removing the lower end of the colon with good results in 33 cases. After surgery the size of the colon diminished as shown by roentgenograms. This operation is certainly a hopeful one now to try out. All others except colectomy seem to have failed.

SUMMARY

In 1922 the writer suggested that since smooth muscle contracts down into a knot when separated from its nearest ganglion cell, the simplest explanation for cardiospasm and the blockage at the distal end of a megacolon would be loss of the ganglion cells in Auerbach's plexus. Since then a number of pathologists have found the expected loss of ganglion cells whenever they have looked for it. It would appear, then, that this very simple explanation for the partial blockage has been well established.

Attempts in the laboratory to destroy the local ganglia have not been successful because they are so highly resistant to noxious influences.

There is a little evidence to show that injuries to extrinsic nerves of the cardia or colon have some influence on the spasm, but usually it is not great. Sympathectomy for the cure of Hirschsprung's disease has not worked well. The logical operation is to remove the obstructing ring of gut and this has now been done by Swenson, Neuhauser and Pickett with good results.

Man has no ring of thickened muscle at the cardia. Some fishes and the birds that regurgitate their food whole have no cardia. Some animals that hang upside down have a strong cardia—as one would expect. In rare instances, men have no cardia, so that when they lie down gastric juice runs out of the nose.

The suggestion that the cardia is pinched closed by the diaphragm is not well supported by facts.

It is curious that in cardiospasm the ring which is so firmly contracted that it can be dilated only with force, is not hypertrophied and is not reinforced with connective tissue.

In some cases psychic trauma may bring on or reinforce cardiospasm, but it does not explain the rigidity of the cardiac ring. The logical and apparently the best treatment for megacolon is the surgical removal of the obstructing segment of bowel.

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MULTIPLE POLYPOSIS OF THE COLON*

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Diffuse or disseminated polyposis of the colon has long been recognized as a separate and distinct disease entity. It is of interest because of its tendency to affect different members of the same family; it is important because if left unchecked it will eventually cause the death of the patient because of its relationship to malignancy. It imposes a great responsibility upon the physician to insist that the proper diagnostic tests and procedures are carried out on any patient suspected of having this disease and to round up and make a survey of the various members of his family. The economic and financial burdens placed upon the patient by this condition are tremendous.

Single or isolated polyps are a rather common finding but diffuse adenomatosis extending from anus to cecum is a relatively rare condition. It is this condition, and its heredofamilial character, with which we are primarily concerned at the moment. Guptill⁸ in 1947, accounted for 352 cases of multiple polyposis of the colon, including five cases of his own. To this collection seven more cases are added.

Historical: To Menzel goes the credit of first noting this condition in 1721, but Lushka in 1861, according to Mayo and Wakefield¹⁵, gave one of the earliest convincing reports of the disease when he described the case of a thirty year old woman, who had multiple lesions of the colon. Virchow in 1863 gave an accurate pathologic description of the condition in his "colitis polyposis cystica". It remained for Harrison Cripps, in 1882, to show the familial relationship of the condition when he reported three cases occurring in one family. Since that time numerous writers have reported similar families having the same condition.

Classification: The classification of the disease which is most widely accepted is that of Erdmann and Morris⁴. They divide polypi of the colon into (1) the adult or acquired type, which may be single or multiple, and (2) adolescent or congenital type (polyposis intestini). Wessen and Barger²² divide polypi into (1) true polypi, and (2) post inflammatory polypi. This classification makes it clear that for the most part there are two types of polypi of the colon.

Etiology: The real and exciting etiologic factors in familial polyposis are not known. The acquired form of polyps result from chronic ulcerative colitis, tuberculosis, amebiasis, strictures and chronic irritation, as seen in the aged. It is also well recognized that people suffering from various forms of allergy often have polyps of the nasal and sinusoidal mucous membranes, but to say that persons with familial polyposis

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also have some form of allergy which runs in the family would be purely speculative. The relationship might well bear further investigation and study.

This condition has been observed in children as early as two years of age. In this connection the cases presented by McKenney¹⁶ are very convincing. He has observed three families with the disease, twenty-one cases in all and all in their third generation. He calls attention to a woman who had four children by two husbands, all of the children having multiple polyposis. In one instance there were four siblings, the youngest two years of age, all with well established polyposis, the lesions being more advanced in accordance with their age.

Incidence: The incidence of diffuse polyposis in the general population is rather difficult to elicit because of the inconvenience and discomfort of proctoscopic examinations. Furthermore, the presenting symptoms may be so mild or entirely lacking, that the patient may not seek medical advice for many years. The paucity of cases is emphasized by the fact that up to 1947 Guptill⁸ could account for only 352 cases. Mayo and Wakefield¹⁶ state that of the patients examined in the Section of Proctology at Mayo Clinic, four per cent had one or more polyps that could be visualized with the sigmoidoscope and of those with polyps, only 0.04 per cent had disseminated polyposis of the colon.

Pathology: Polyps result from the excessive proliferation of intraluminal masses of various sizes and shapes. They vary in size from 0.5 to 1 mm. in diameter to as large as 2 to 6 cm. in the large pedunculated polyps. They may be villous, sessile, or pedunculated. At first they represent increased glandular proliferation with round cell infiltration. Then the submucosal stroma and connective tissue push forth and create a central core for the growth. At the same time the acini and columnar epithelial cells ramify in a tree-like fashion, the cells becoming distended, and show pseudo-mucin or colloid degeneration. As malignant changes supervene, the mitotic figures become more abundant with atypical and dark staining nuclei. Still later the cells invade the stromal connective tissue and basement membrane until the full blown picture of adeno-carcinoma blossoms forth^{2, 3, 8, 9, 10, 19}.

As pointed out by Mayo and Wakefield¹⁶ these polyps may prove to be serious in one of four ways; (1) They may bleed as a result of infection or ulceration; (2) they may cause obstruction when large enough; (3) they may produce an intussusception; and (4) most important of all, they may undergo malignant change.

Relationship to malignancy: The relationship to malignancy is very definite and clear cut, and forms the basis for the radical surgical treatment of this disease. Ewing, as quoted by Hedin⁹ and Cattell¹, states that "nowhere else can the change from normal mucosa to inflammation, gland cell hypertrophy, adenoma and adeno-carcinoma be so clearly demonstrated as in multiple polyposis of the colon." According to Lockhart-Mummery,¹⁴ "almost all recorded cases of multiple polypi of the colon eventually become malignant." Estes,⁵ and Pugh and Nesselrod²⁰ believe that one hundred per cent eventually become malignant.

Symptoms: Various writers have tabulated and analyzed the symptoms in their series^{9, 10, 19}. The symptoms of polyposis intestini are remarkable in that they may be entirely lacking and the onset of the disease may be entirely insidious. This is

well illustrated in three of the cases cited herein, and must be borne in mind when making a survey and speaking to the family of a patient with diffuse polyposis. Different writers have called attention to the fact that malignant degeneration may have taken place before the patient presents himself for treatment. The commonest symptoms are those associated with irritation of the colon; namely diarrhea, passage of blood in stools and passage of mucous. Often the patient will complain of nothing more than one or two loose bowel movements extending over a period of one or two years. Anorexia, weight loss, fatigue are frequent complaints. Mild abdominal cramp-like pains are due to segmental spasms and partial obstruction.

Diagnosis: Diagnosis is made by rectal examination, proctoscopic and sigmoidoscopic examination and barium enema double-contrast x-rays. Of the three, the air injection post-evacuation films are the most important, for this will show the mucous membrane studded with polyps throughout the course of the colon and give evidence of the extent of the pathology.

Treatment: The treatment of this condition is strictly surgical and is aimed at the elimination of the entire mucosa-bearing area of the colon. Surgical procedures along the same lines and with the same ends in view have been worked out by numerous surgeons.^{14, 11, 21, 9, 15, 19, 20, 5} In this connection Hedin⁹ poses some interesting and pertinent questions. To quote; "These conditions are often seen in young individuals who are otherwise healthy. To recommend a radical procedure, such as a colectomy, imposes on the surgeon a great responsibility and on the patient a great danger. In many of the cases most of the colon is normal from a clinical standpoint. And who, in our present state of knowledge of this disease, is in a position to say that the entire colon should be sacrificed? In this connection one is confronted with many perplexing questions. How long have the polyps been present? Is a colon, in which only a segment is involved, destined in time to become studded with polyps? Or will malignancy and death occur before sufficient time has elapsed for the disease to involve the entire colon? Is the heredofamilial factor present to the same degree in both types? If this is so, why are polyps discovered so frequently at autopsy in the aged? Are polyps found late in life all on an inflammatory basis or have they been present since birth? Could all polyps of the colon be caused by an organism which so far has not been isolated?"

These questions were raised in 1939. Since then enough evidence has been accumulated to clearly indicate that total colectomy, is not only justifiable, but that without such a procedure the patient will in all likelihood die of carcinoma around the age of forty.

In eliminating the mucosa-bearing area of the colon the pendulum has swung towards a 2 stage operation which includes fulguration of the polyps in the recto-sigmoid, followed by an ileosigmoidostomy and a colectomy above the anastomosis. Toward this end the rectum and sigmoid as far as possible are

cleared of polyps by repeated fulgurations. The number removed at each sitting depends upon the endurance of the patient, health of the mucous membrane and the number of polyps to be removed. No anesthesia is employed since the mucous membrane is insensitive to the removal of the polyps and full cooperation of the patient is desirable.

The patient is allowed to go home and have a period of rest and recuperation and build up the bodily resistance prior to colectomy. After about six weeks the patient returns and is again sigmoidoscoped to ascertain the condition of the mucous membrane. If satisfactory, ileorectosigmoidostomy is performed, which is followed by colectomy as soon as the patient's condition permits.

Before any attempts are made to save the rectum, proper steps are taken by means of biopsy to make sure than the original polyps are benign. If any evidence of malignancy is found, a permanent ileostomy must be resorted to, followed by a total colectomy and a posterior resection of the rectum.

If an ileorectosigmoidostomy is employed, the patient is followed every six months, or sooner if symptoms intervene, to note the possible recurrence of polypi which are fulgurated if found. The full understanding and cooperation of the patient must be had in order to affect a cure.

This method of treatment is particularly desirable in younger patients, as many of them are, since it preserves normal evacuation. In time the bowel habit returns to normal with as few as two well formed stools daily.

The following case reports bring out the prominent features of this disease. All patients were seen on the surgical service at St. Luke's Hospital, Bethlehem, Pennsylvania.

CASE HISTORIES

Case 1. Mrs. A. M. Age 37. Admitted May 11, 1928. For the past year patient had been bothered with "internal hemorrhoids" and rectal bleeding. She had lost a considerable amount of weight during past year. She came into the hospital with acute intestinal obstruction and pain in the left lower abdomen, of about one week duration. Had become increasingly constipated, the last bowel movement being two days before admission. Pain had been persistent during this time. The abdomen was hugely distended and tympanitic throughout, more pronounced on the left side.

On May 12, 1928 an emergency colostomy was performed, following which on May 30, 1928 an anterior resection of the sigmoid was performed for an obstructive adenocarcinoma. At the time of operation polyps were palpated in the descending colon. The surgical specimen showed a benign polyp just proximal to the adenocarcinoma. The patient made a slow recovery and was discharged on September 6, 1928.

She was readmitted July 2, 1931 with the chief complaint of pain in the lower abdomen and extremities and loss of weight. An exploratory celiotomy was performed on July 9, 1931, at which time a large caseous tumor mass was found in the mesentery

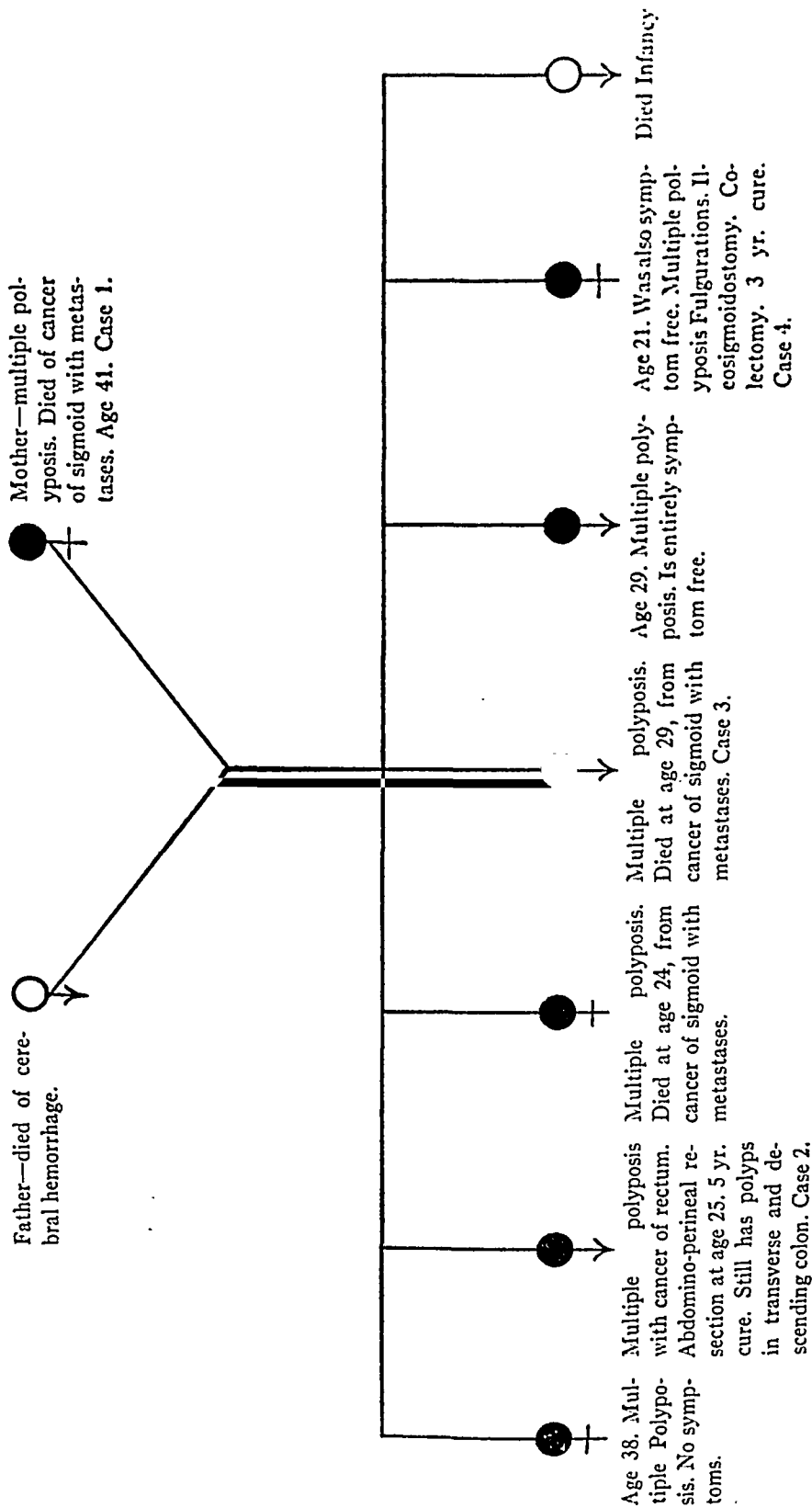


CHART 1. DEPICTING FAMILY TREE OF POLYPOSIS FAMILY

of the ileum and transverse colon. The mass was adherent to the abdominal wall and there were numerous peritoneal implants. The patient went into surgical shock and died the day of operation. Autopsy showed generalized carcinomatosis.

Case 2. Mr. C. M. Age 25. Son of Case 1. Admitted November 3, 1942. Three months previously patient first noticed blood in his stools and pain on defecation. There was no anorexia and no loss of weight. His family history was negative except for the fact that his mother died of cancer of the large bowel at the age of 41.

His abdomen was soft and flat and without any evidence of spasm. No masses palpable. On rectal examination an ulcerating mass was found on the anterior wall just within the sphincter which was confirmed by proctoscopic examination. Also noted were numerous bleeding sessile polyps in the rectum and sigmoid colon. Biopsy of the ulcer showed adenocarcinoma Grade II. B.P. 118/74. R.B.C. 5,000,000. Hb. 14 gms. W.B.C. 9,200.

On November 11, 1942 an abdominal perineal resection of the rectum and sigmoid was performed creating a permanent colostomy on the left. The ulcerating lesion on the rectal wall was 4 cm. in diameter and on microscopic examination proved to be adenocarcinoma Grade 2. Numerous polyps were again noted in the entire rectum and sigmoid. There was no evidence of metastasis in the regional lymph nodes. He was discharged December 17, 1942 in good condition and with a granulating perineal wound.

Follow up x-ray of the colon showed multiple polyposis of the transverse and descending colon. The patient had gained thirty-five pounds in weight, had since married and refused further treatment.

Case 3. Mr. M. M. Age 29. Also a son of Case 1. Admitted February 1, 1944. Loss of appetite, weakness, loss of weight (about forty-five pounds) of about six months duration. Patient suffered a compound fracture of the right tibia in December 1942 spending sixteen weeks in the hospital. Eight years previously he had a benign polyp removed from the rectum at another hospital, and was told that he had multiple polyps of the rectum and sigmoid. He had no nausea, vomiting, or blood in the stools but did mention occasional bouts of diarrhea.

Operation on February 7, 1944 revealed a carcinoma of the sigmoid without obstruction; there were numerous enlarged retro-peritoneal glands with metastasis to the liver. The mass in the upper abdomen being the result of the large liver. Biopsy of a nodule showed adenocarcinoma. The patient died at home on April 28, 1944. No autopsy.

Comment: The incidence of multiple polyposis and carcinoma of the colon was now very evident and outstanding and the importance of surveying and examining the remaining members of this family became imperative. With this in mind a thorough investigation was undertaken and the results are depicted in chart 1 showing the family tree. After some persuasion the following member of the family was hospitalized.

Case 4. Miss D. M. Age 22. Daughter of Case 1. This patient was symptom free and without complaint. She was proctoscoped and multiple discrete polyps of the rectum and sigmoid were noted. Barium enema in March 1944 revealed multiple

polyposis of the transverse and descending colon. (Figures 1 and 2.) These polyps were destroyed by repeated sigmoidoscopy and fulgurations, with the intention of doing an ileorectosigmoidostomy and total colectomy at later dates.

Admitted to hospital July 9, 1944. Patient was a moderately obese, young woman, in excellent health. R.B.C. 4,500,000. Hb. 12 gms. W.B.C. 7,700. On July 14, 1944 an ileorectosigmoidostomy was performed with the removal of more polyps at the site of anastomosis. At operation numerous polyps were palpated in the transverse and descending colon. Discharged July 27, 1944.



FIG. 1. Post-evacuation double contrast studies of Case 4 showing polyps in hepatic flexure and upper part of descending colon.

Readmitted October 30, 1944. She had lost twenty-one pounds in weight since operation in July. She had occasional gastrointestinal upsets but appeared to be in good health. R.B.C. 4,100,000. Hb. 12.5 gms. W.B.C. 9,000. On November 3, 1944 colectomy was performed from the distal ileum down to the anastomosis at the rectosigmoid. The mucous membrane was covered with polyps from cecum to sigmoid. One large polyp was encountered in the transverse colon just beyond the hepatic flexure. Microscopic examination revealed the tumor to be pre-malignant. Discharged November 16, 1944.

Three years later she was still in good health experiencing only an occasional abdominal pain. She has had repeated check-ups and fulguration of rectal and sigmoidal polyps. The anastomotic site is easily visualized. Routine examinations every six months recommended to patient.

This case represents more or less the preferred form of treatment in that the normal outlet was maintained while at the same time removing or destroying the diseased



FIG. 2. Post-evacuation double contrast studies of Case 4 showing polyps in transverse colon and lower portion of the descending colon.

mucous membrane. This is especially desirable in younger individuals where the life expectancy is greater. The follow up care, however, must be most vigilant.

Further investigation completed the medical history of this polyposis family. Some were examined as out patients, others were seen and treated at distant points.

The eldest is a daughter, age 35, married and has two children. She was symptom free and had normal bowel function. Rectal and proctoscopic examination was negative for polyps and new growths up to mid-sigmoid. Barium enema revealed multiple

polyposis of transverse and descending colon. The situation was explained to the patient, but she refused surgery on economic grounds. Three years later she was still symptom free, and repeat x-ray confirmed the presence of the polyps. One polyp removed from sigmoid by fulguration proved to be benign.

Another daughter, age 24, single, had a six months history of increasing weakness, loss of appetite, bouts of abdominal pain and occasional diarrhea. At operation she was found to have a carcinoma of the sigmoid with polyps in the descending colon and sigmoid, along with intraperitoneal implants of the carcinoma. She died three months later; no autopsy.

The remaining member of the family was a son, age 20, single. He also was symptom free and had normal bowel function. Bowels moved three to four times a day. Rectal examination revealed one palpable polyp. Proctoscopy showed numerous sessile polyps, four to eight mm. in diameter, up to mid-sigmoid. Barium enema refused.

The seventh member of this family was a male who died in infancy.

DISCUSSION

A review of the medical history of this remarkable family brings out the salient features of multiple (diffuse, disseminated) or familial polyposis of the large intestine. It shows how the disease manifests itself early in life and the definite tendency toward early malignant change. It brings out the point that patients with this condition may not present themselves for treatment until the complications incident to malignant change are manifest. On the other hand patients may be entirely symptom free, the diagnosis being made on routine check up because of the suspicious family history. This fact is forcefully brought out in three instances of this family.

The fact that more than one member of this family was so afflicted is not merely coincidental; instead it lends support to the impression of more than three-hundred and fifty recorded cases that this disease has a strong familial predisposition. No member of such a family can be declared free of the stigma until thorough studies have been carried out—including rectal, sigmoidoscopic and barium enema double-contrast x-rays.

The treatment of this condition depends somewhat on the age of the patient, the progression of the lesions and the prospective cooperation of the patient. If any malignant changes are noted in the recto-sigmoid, it should be sacrificed by all means. If the rectum is spared, repeated proctoscopic examinations and fulgurations are done every six months or sooner if symptoms intervene.

CONCLUSIONS

1. Multiple polyposis of the colon is a disease entity which tends to run in families and which has a strong tendency to become carcinomatous.
2. The disease is often insidious at onset but can be diagnosed by rectal, sigmoidoscopic and barium double-contrast enemas.
3. Because of the familial tendency and the high percentage of malignant

changes it is imperative that all members of a polyposis family be given thorough and repeated investigations before they are given a clean bill of health.

4. The treatment is aimed at the elimination of the mucous membrane bearing areas of the colon, with the possible exception of that portion which can be repeatedly examined, namely the recto-sigmoid.

5. A family history has been presented which illustrates the main characteristics of this disease.

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INCREASED ACTIVITY OF THE INTESTINES FOLLOWING INJECTION OF EPINEPHRINE

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The response to epinephrine of isolated smooth muscle taken from any part of the gastrointestinal tract, is well known. A review of the literature reveals no reference to the supernormal phase following the typical depression. Concerning this matter, Alvarez¹ writes: "To be sure, we speak of certain purgatives as acting principally on the small bowel or on the large, but on reading extensively on the subject, I could find no statement suggesting that anyone had puzzled over the fact that an intestinal sedative such as epinephrine can produce purgation."

We have often observed in work on intestinal motility, as well as in experiments carried out in the laboratory by students, that following the depression of the intestine by epinephrine there is a period of supernormal activity. During this period not only is the tonus increased, but the rhythmic movements often are more frequent, and seem to be stronger. This has been observed in situ as well as in isolated gut preparations (Figures 1 and 2). It would appear as if this supernormal activity is independent of the intestinal gradient since it can be demonstrated in small as well as in large intestine (Figure 3).

It has been possible to demonstrate this supernormal activity in segments of intestine suspended in a muscle chamber, in oxygenated Ringer's solution, recording the movements of the longitudinal muscle only. However, when a piece of gut is suspended in oxygenated Ringer's fluid using the method of Trendelenburg², this supernormal activity was observed in the circular coat as well. When movements of the gut are recorded in situ utilizing the method of Roger, as modified by Dreyer³ it has been possible to demonstrate this increased activity in the small and large intestine. Similar observations have been repeatedly made following stimulation of the splanchnic nerves. The depression of the small intestine following injection of posterior pituitary extract is also followed by a period of greater activity.

The following experimental evidence indicates that this heightened activity is due to increased excitability of the muscle. Stimulation of the peripheral end of the cut vagus with a submaximal current causes an increase in tonus and motility. This can be reproduced on repeated stimulation of the sectioned vagus. If the vagus be stimulated during the period of heightened activity following epinephrine, a greater percentage increase in tonus and motility is noted.



FIG. 1. Cat 2.2 Kg. Anesthesia—Chloralose 100.0 mgm/kg. Adrenals removed. Jejunum in situ.



FIG. 2. Kitten Jejunum (isolated). 1. Longitudinal muscle. 2. Circular muscle. 5.0 cc bath of Ringer Solution.

This increased activity of the bowel following depression from certain drugs or stimulation of the sympathetic nerves would seem to account for the heretofore unexplained purgation following the use of these drugs.

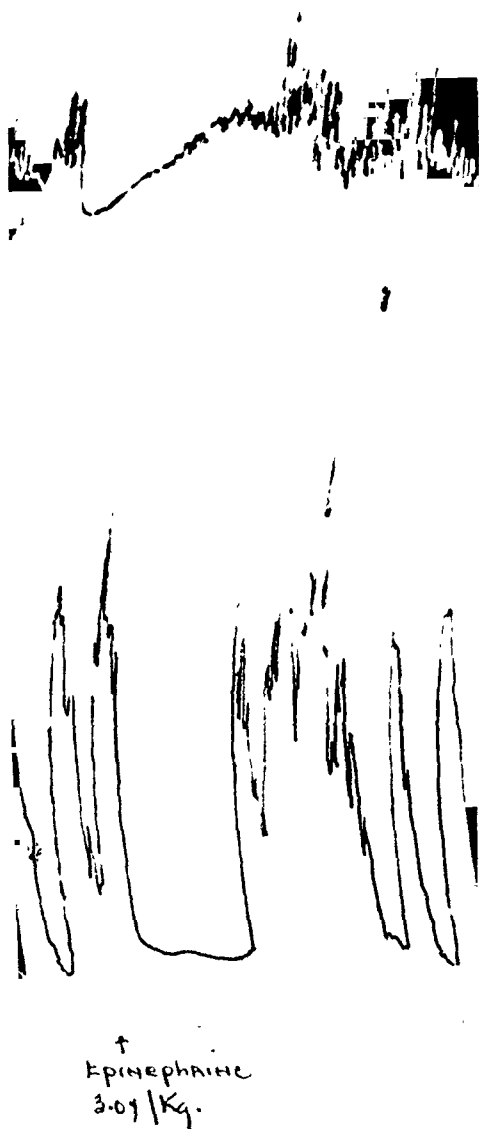


FIG. 3. Cat 3.8 Kg Intestine in situ. Anesthesia—Chloralose 100.0 mg./kg (upper) Jejunum and proximal colon. (lower)

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THE EFFECT OF DIBUTOLINE ON THE MOTILITY OF THE STOMACH AND SMALL INTESTINE IN MAN— AN X-RAY STUDY*

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INTRODUCTION

It has been shown that dibutoline (the dibutylurethan of dimethylethyl-B-hydroxyethyl ammonium sulfate) has a marked parasympatholytic effect¹⁻¹⁰. It blocks the usual response to acetylcholine at effector cells innervated by post ganglionic nerves and also has a direct inhibitory action on nonstriated muscle. In experimental animals, it has been demonstrated to relax the iris constrictor and the ciliary muscle, to inhibit the submaxillary salivary gland, and to relax smooth muscle in arterioles and in the gastro-intestinal, biliary, and urinary tracts. Apparently, it has no effect upon the sympathetic nerves. The purpose of this study was to determine the effect of this drug on the motility of the stomach and small intestine in man, as demonstrated by x-ray.

METHOD

The 10 subjects used in this study had no evidence of disease of the gastro-intestinal tract. The esophagus, stomach, and small intestine were examined by fluoroscopy and by roentgenogram at the time of ingestion of the barium meal and at intervals of 1, 2, 4, and 6 hours thereafter. This procedure was repeated in each case several days later while the patient was receiving dibutoline subcutaneously. The dosage varied from 10 mg. q. 4 h. to 25 mg. q. 1 h., and the number of doses varied from 4 to 30. All but one of the 10 patients received the injections throughout the course of x-ray study. The tenth patient, however, was given the drug for 4 hours only and was then studied for 4 hours longer to determine the length of its action. In one patient who was given 25 mg. q. 1 h., a loop of jejunum was studied by fluoroscopy and by roentgenography for changes in the mucosal pattern. In two subjects, studies as detailed above were carried out later, substituting atropine sulfate, 0.6 mg. q. 2 h. subcutaneously, for dibutoline, in order to compare the effects of the two drugs.

* We wish to express our appreciation to the Merck Company, Rahway, New Jersey, who furnished the Dibutoline for this experiment.

This study was supported by a grant from the John and Mary R. Markle Foundation.

† Now located at Mesa, Arizona.



FIG. 1

A. Top row: Films at 1, 2, 4, and 6 hours after the ingestion of barium showing the stomach empty and most of the meal in the ascending colon by 4 hours.
B. Bottom row: Repetition of the study in the same patient while receiving dibutoline, 20 mg. subcutaneously at hourly intervals. At 6 hours, most of the barium is still in the stomach; the duodenum is filled, and the head of the barium column is in the proximal ileum.

RESULTS

No effect of dibutoline upon the esophagus was observed in these 10 patients. The motility of the stomach and small intestine, however, was profoundly

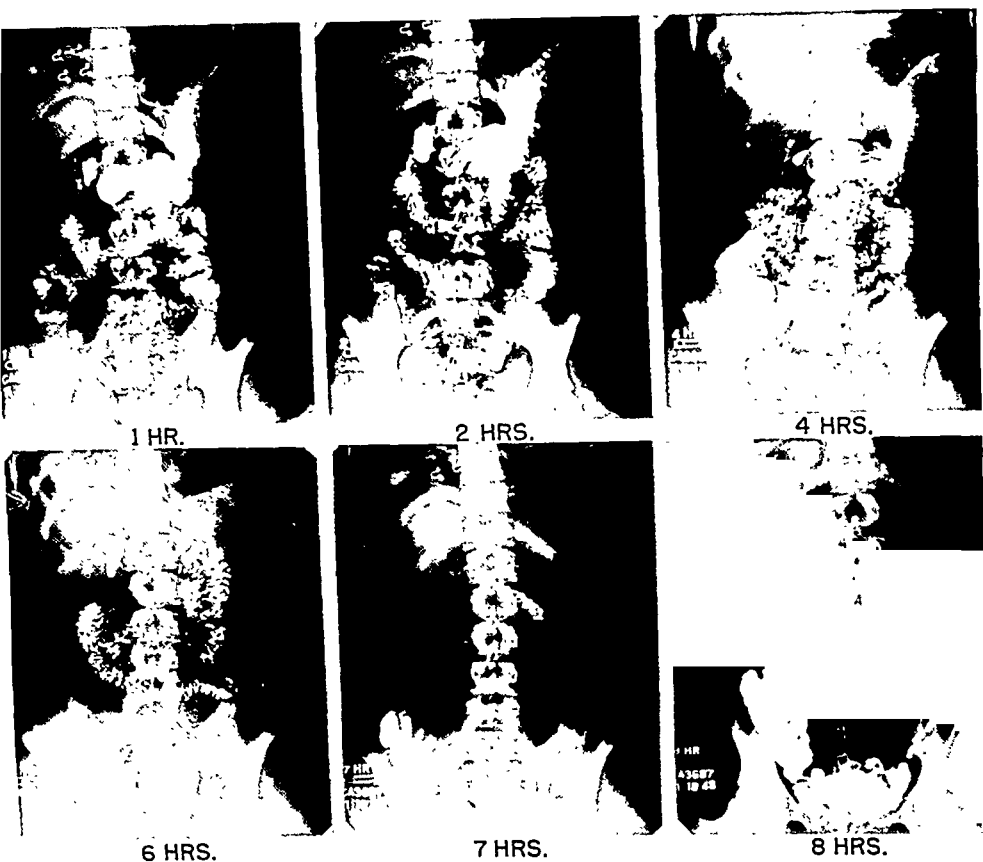


FIG. 2

A. Top row: Films at 1, 2, and 4 hours after the ingestion of barium while the patient was receiving dibutoline, 25 mg. subcutaneously at hourly intervals. At 4 hours, most of the barium is in the stomach, and the head of the barium column is in the proximal ileum.

B. Bottom row: Films at 6, 7, and 8 hours after the ingestion of the barium meal in the same patient after discontinuing the drug. They show the rapid resumption of activity of the stomach and small intestine and at 7 hours all of the barium is in the terminal ileum and ascending colon.

altered. The stomach showed marked diminution in peristaltic activity, but in no case was peristalsis completely abolished. There was no dilatation or change in the general contour of the stomach, which appeared to be at rest with preservation of normal tonus. After large doses, there was a marked delay in emptying. (Figure 1)

The duodenum filled well in each case and barium remained there for a variable period of time, in some cases as long as 6 hours. As in the stomach, peristalsis was diminished but not absent. A definite increase in the caliber of the lumen was a constant finding, but no abnormality in the mucosal pattern was observed.

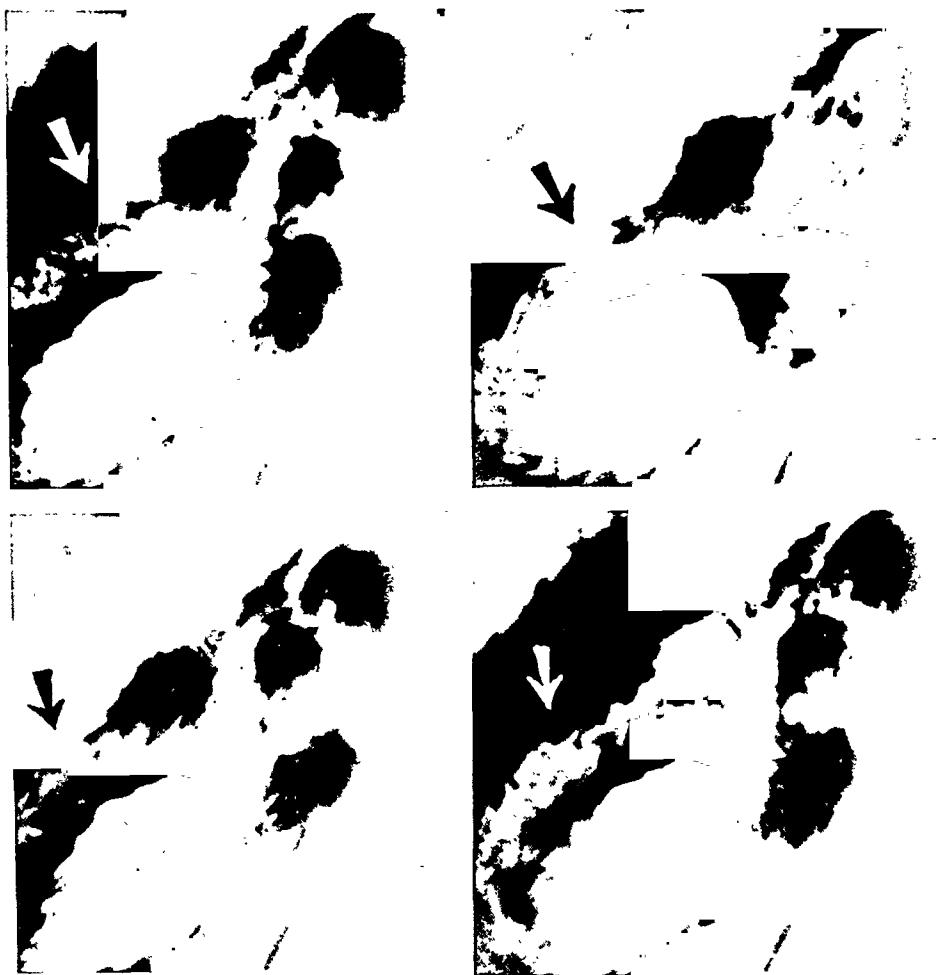


FIG. 3. Films of a loop of jejunum taken in rapid succession 2 hours after the ingestion of barium while the patient received dibutoline. Note the change in the mucosal pattern in the absence of propulsion, associated with change in the caliber of the lumen.

There was a striking prolongation of transit time of barium through the small intestine. In only one instance did the barium reach the cecum within 6 hours and in the majority of cases barium did not progress beyond the proximal ileum within this period. There was a pronounced increase in the caliber of the intestine and lengthening of the individual segments. Peristaltic contractions were meager but never abolished entirely, and no appreciable abnormality in the mucosal pattern was noted. The drug exhibited a very rapid action, patients noting dryness of the mouth within two to three minutes after its subcutaneous

administration. As can be seen in Figure 2, the effect of the drug was dissipated within two to three hours. Atropine had effects similar to those of dibutoline on the two patients in whom both drugs were used, but the side reactions were more marked. Figures 3 and 4 illustrate definite changes in the mucosal pattern of the jejunum in the absence of propulsion of the barium column.

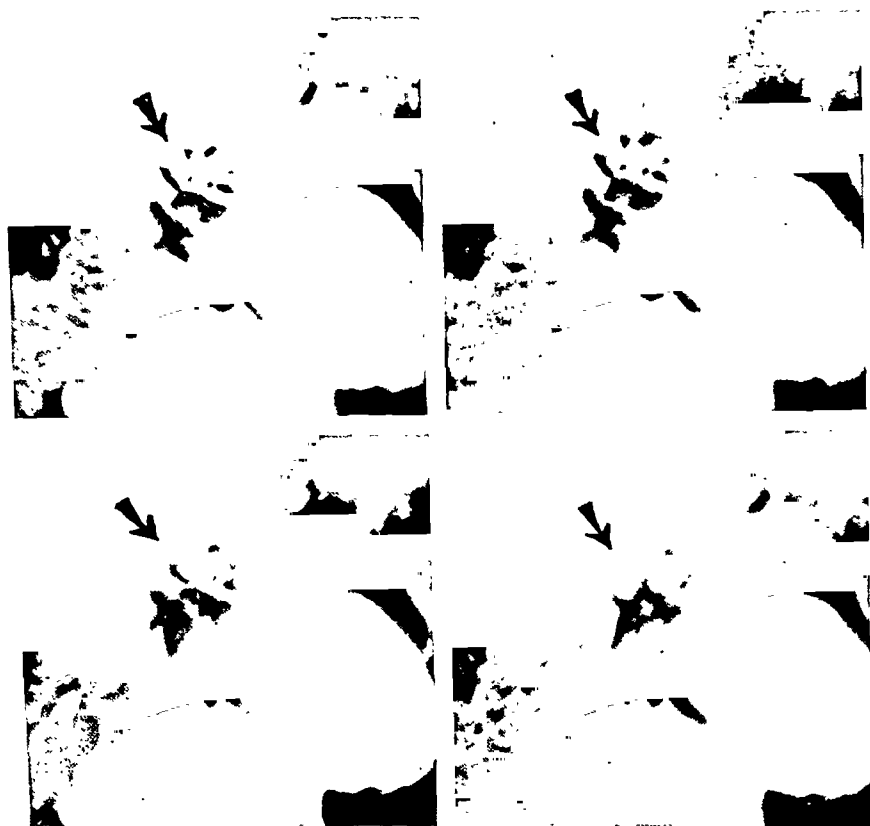


FIG. 4. Films of a loop of jejunum taken in rapid succession 2 hours after the ingestion of barium while the patient received dibutoline. Note the slight change in mucosal pattern apparently in the absence of change of the caliber or general configuration of the segment.

Side effects of the drug were mild, being noted in only six cases, and consisted of dryness of the mouth and visual impairment, with flushing of the face in one patient. They were not constantly related to the size of the dose, but in general were more pronounced in subjects receiving the larger amounts.

DISCUSSION

The search for a more effective antispasmodic and parasympatholytic drug continues. In investigating the parasympatholytic properties of dibutoline in

normal persons, striking alteration in the radiologic patterns in the stomach and small intestine has been demonstrated. The more marked effects, as shown in Figure 1, are thought to represent almost complete block of parasympathetic stimulation. The pronounced changes in the small intestinal pattern serve to emphasize the importance of the role of autonomic control in intestinal physiology.

Two definite types of small intestinal movement have long been recognized. The first are rhythmic segmental contractions thought to be important in absorption and the second are propulsive movements. In addition, it has been

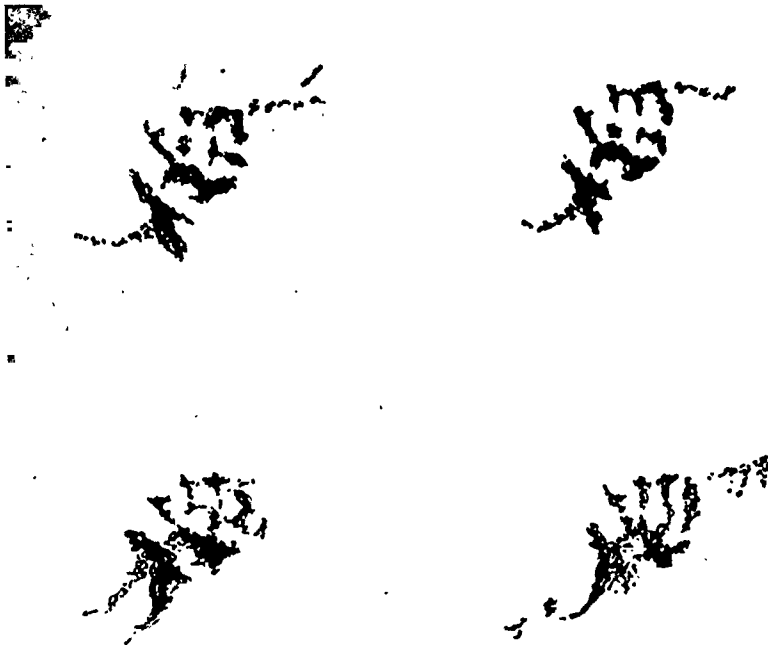


FIG. 5. Tracings of the mucosal patterns in segment of jejunum shown in Figure 4 to illustrate the changes more clearly.

suggested by the physiological studies of King and Arnold and by the radiological studies of Forssell and of Golden that the mucous membrane may move freely and independently of the tunica muscularis.¹¹ Forssell has further suggested that the movements of the circular and longitudinal layers of the tunica muscularis are under parasympathetic control whereas those movements of the muscularis mucosa are dependent upon sympathetic stimulation. The studies of Holt et al.^{12, 13}, with tetraethylammonium chloride shed considerable light on the problem. They demonstrated complete cessation of all intestinal movement following the intravenous injection of the drug which blocks both sympathetic and parasympathetic impulses at the ganglia. Careful study of

Figure 3 in our report shows the change in the mucosal pattern to be accompanied by change in the size of the lumen. This would indicate a concurrent segmental contraction produced by the tunica muscularis. Propulsion did not occur, however, because the jejunal loop was filled 2 and $\frac{1}{2}$ hours later as demonstrated by a subsequent x-ray. Figure 4, shows slight though definite changes in the absence of caliber change. This may be due to independent movement of the mucosa, though it is conceivable that the changes illustrated may be caused by respiration or by cardiovascular pulsation, resulting in re-distribution of barium in the segment. Therefore, dibutoline caused a paralysis of propulsion with preservation of segmental and mucosal movements. There is a possibility, however, that larger doses of the drug might have abolished these movements likewise.

The ideal parasympatholytic drug should have an immediate effect, a prolonged action and minimal side reactions after oral administration. Dibutoline has an immediate though transient effect and minimal side reaction but unfortunately is not effective when given by mouth in doses thus far employed⁷. Therefore, the clinical application of the drug would be limited by the above factors. Marquardt et al.¹⁴ have used it clinically in various disorders of the gastrointestinal tract such as colonic spasm, diverticulitis of the colon, chronic non-specific ulcerative colitis, and peptic ulcer and report excellent results.

CONCLUSIONS

1. Dibutoline when administered subcutaneously to normal humans exhibits a marked parasympatholytic effect manifested by a profound inhibition of peristaltic activity of the stomach and small intestine as demonstrated by x-ray.
2. The side effects of the drug in the doses used were minimal and of no consequence.
3. Its action is rapid in onset, of short duration, and follows parenteral administration only.
4. Dibutoline abolishes propulsive movements, decreases segmental movements, but changes in mucosal pattern continue.

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Case Reports

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ADENOMATOUS POLYPOSIS OF THE WHOLE GASTROINTESTINAL TRACT

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The rarity of multiple adenomatous polypi of the stomach, entire small intestine and cecum as a simultaneous occurrence justifies publication of such an unusual instance.

CASE REPORT

Miss S. L. B. (G-12701), a 19 year old stenographer, was initially seen and hospitalized June 29, 1946. Generalized abdominal cramping pain, nausea, vomiting, weakness and concomitant twenty-five pound weight loss characterized an acute illness of twenty-eight days duration. Watery diarrhea of the first twenty days was followed by obstructive phenomena. Fecal vomiting developed prior to admission.

There was a probable brief episode of obstruction when eighteen months of age. In 1934, at seven years of age, acute high obstruction necessitated exploration. Gangrenous terminal ileal intussusception required resection of thirty-six inches of ileum. The surgeon reported polyposis of the ileum. An inadequate pathological study of this specimen reported hemorrhagic infarction without further comment.

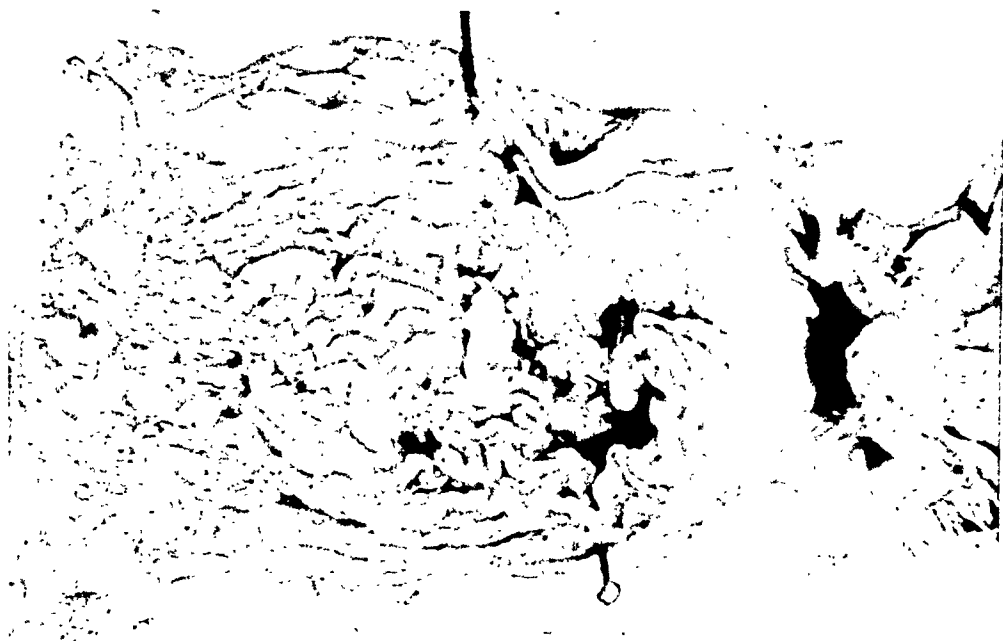
Three weeks thereafter the patient was again hospitalized for right flank pain. The discharge diagnosis of a urinary calculus seemed inadequately confirmed.

After a six month asymptomatic period the patient experienced recurrent obstructive phenomena relieved by non surgical measures. Gastrointestinal series on this occasion revealed a barium displacing defect in the duodenal cap presumed to be a gastric polyp prolapsing through the pylorus. The patient deserted the hospital before conclusive studies were made. There was no recurrence until the present study.

On examination the findings substantiated an impression of low small bowel obstruction. There was generalized abdominal tenderness, accentuated in the cecal area. There were two palpable masses in the right lower quadrant.

Clinically, the patient had a partial low intestinal obstruction. Her general condition contraindicated immediate surgery. On July 7th, exploration by Dr. Howard Mahorner revealed two sites of intussusception, ileo-cecal and ileo-ileal. Search of the small bowel revealed polypi throughout. The ileo-ileal intussusception was reduced. The ileo-cecal segment was resected after an unsuccessful attempt to reduce the intussusception. Four of the larger polyps were extruded and excised from the lumen of the ileum.

The patient expired, on the fifth postoperative day, after a pulmonary infarct.



Polypi in the Gastric Segment



Polypi in the Proximal jejunum

On necropsy innumerable pedunculated polyps were found involving the gastrointestinal tract from the cardia of the stomach through to the cecum. There were approximately one hundred and eighty polyps varying from 3 mm. to 4 cm. in diameter. Nine were within the gastric lumen. There were seven in the duodenal segment.



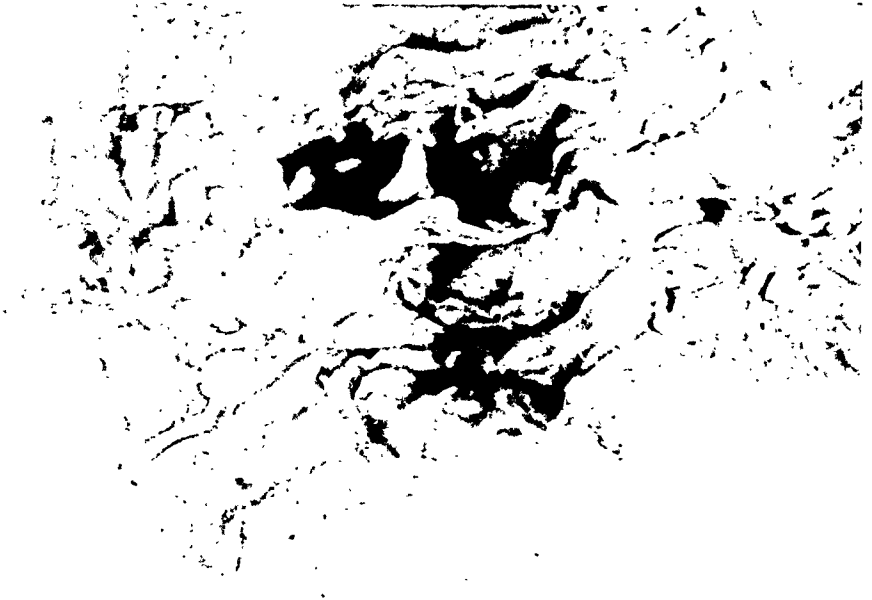
Polypi in the distal jejunum



Polypi in the ileum

The jejunum contained ninety lesions but many of the polypi were so small that accuracy was difficult. In the remaining ileal segment there were sixty-nine polypi and five in that portion of the ascending colon studied at autopsy. Microscopically these polyps showed "numerous glandular acini, many of which were cystic, lined by

adult columnar epithelium containing small globules of mucus within the cytoplasm of the cell. The nuclei were basilar in location. The supporting connective tissue showed infiltration with lymphocytes and plasma cells. There was no evidence of malignancy in any of the polyps examined."



A single large polyp in the ascending colon

COMMENT

Polyposis of the colon is relatively common; involvement of all gastrointestinal segments is exceedingly rare. Bockus reports one case with polypi in both the stomach and the small bowel¹. Ravitch, including his own case, reported three well documented instances where the entire gastrointestinal tract from cardia to anus was involved with adenomatous polyps. In addition, he collected ten other cases in which there was concomitant involvement of each segment of the gastrointestinal tract beginning with the stomach².

Variation in terminology probably accounts for the conflict in reports on the incidence of polypoid adenomatosis. The term "polypoid adenomatosis" is applicable when the mucosa of an entire gastrointestinal segment is studded with "innumerable, discreet, lobulated, pedunculated, often cystic tumors, each with its individual attachment" to the mucosa (polyadenomes polypeaux). Pseudopolyposis or "polyadenomes en nappe" designates those innumerable flat closely arranged elevations of the mucous membrane which are thought to be the result of mucosal hypertrophy or hyperplasia¹. Mentrrier used this terminology in classifying such changes in the stomach; it seems applicable to any segment of the gastrointestinal tract¹.

The etiology of polypoid adenomatosis is obscure. Anderson and Tovell² suggest coordinating the congenital, inflammatory and nervous or hormonal factors by designating one primary and the other a releasing factor. While diffuse colonic involvement is often familial, occurrence elsewhere in the gastrointestinal tract rarely conforms in this respect².

All ages are susceptible, there is no racial or sexual predilection^{4, 5}.

The occurrence of carcinomatous change in gastrointestinal adenomatous polypi is significant.

These reports show too wide a variance, the potentiality of a benign polyp becoming malignant is an accepted eventuality. Boyd, estimating a malignancy incidence of 5% in single adenomatous polyps, indicates the total "incidence of carcinoma is directly proportional to the number of papillomata"¹⁰.

TABLE I

SITE	CARCINOMATOUS CHANGE
Stomach	18% (6) 12% (7)
Small bowel	6.6% (6) 26.6% (8)
Colon	5-85 (9)

No correlation between polyp size and malignant potentiality exists. Determination of malignancy or benignancy of course anticipates histological serial section of every polyp. Obviously, where the polyposis is extensive, the task becomes almost endless.

Polypi may be asymptomatic³. Size, number, structure, pedicle length and location, each may determine the presenting symptomatology. Unless complicated a palpable tumor mass is exceptional³. At exploratory the tumors may not be palpable through the bowel wall. Intussusception produced by polyposis of the small bowel is a frequent and dramatic indication⁸. Hemorrhage may be an intermittent, mild or severe manifestation^{3, 11, 12, 13}.

Unexplained gastrointestinal symptomatology and especially anemia, hematemesis, melena, diarrhea, constipation or achlorhydria should stimulate a search for polypi^{2, 4}. X-ray, gastroscopy and sigmoidoscopy are eliminative diagnosis procedures.

SUMMARY

1. An unusual case of adenomatous polyposis of the stomach, small bowel and cecum is reported.

2. The importance of proper terminology is stressed.
3. Carcinomatous transformation as a potentiality of all polypi is emphasized.
4. Although the symptomatology is protean, intussusception and hemorrhage are frequent.
5. Unexplained gastrointestinal symptomatology necessitates an eliminative study for polypi.

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CYTOLOGIC EXAMINATION OF SEDIMENT FROM THE ESOPHAGUS IN A CASE OF INTRA-EPIDERMAL CARCINOMA OF THE ESOPHAGUS

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A study of the cytology of gastric sediment was initiated at the Graduate Hospital of the University of Pennsylvania in September 1948 in conjunction with the Gastrointestinal Service. Patients with gastrointestinal complaints were selected in an attempt to provide information complementary to that obtained by roentgenology and gastroscopy in the early diagnosis of gastric malignancy. To date, we have completed studies on 50 patients with gastrointestinal symptoms. In one study a unique circumstance prevented us from obtaining gastric residuum, but the outcome stimulated us to examine the cytology of the desquamated epithelium aspirated directly from the esophagus.

HISTORY

This 63 year old, white laborer was referred to the Graduate Hospital on 10/10/48 with a diagnosis of gastric neoplasm on the basis of roentgenologic study. He complained of dysphagia and vomiting that began about November, 1947 when he noticed that "food seemed to stop just as it entered the stomach." The frequency of vomiting increased, and during the two months prior to his admission all foods except liquids produced vomiting. He had a feeling of a lump in the upper epigastrium after eating, but denied any pain. In the previous year there had been a weight loss of 30 to 35 pounds, most of which had occurred in the last three months; at that time he tired easily and was much weaker. He denied hematemesis.

For many years he had had a chronic cough, and in the past 3 years coughing induced some shortness of breath.

The patient appeared thin and wasted, but in no pain. He was not dyspneic in the dorsal decubitus position. There were many shotty inguinal nodes bilaterally; none could be palpated in the neck. The thoracic cage appeared to be emphysematous but auscultation and percussion were normal. The abdominal and rectal examinations were negative.

Examinations of the blood showed a red count of 4.61 million, hemoglobin of 13.5 grams per 100 cc., hematocrit of 40%, white count of 5,800, sedimentation rate of 7 mm., prothrombin time of 84% of normal, negative serology, total proteins of 5.20 grams per 100 cc. with albumin of 3.32 and globulin of 1.88, and blood urea nitrogen of 19 mgm%. Two examinations of sputum were negative for acid-fast bacilli. The stool gave a doubtful reaction for the presence of occult blood. The urinalysis was within normal limits.

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On October 11, 1948, a roentgenogram of the chest was reported as "probable minimal primary tuberculous infection of the right infraclavicular area. The left costophrenic sulcus was obscured."

A cytologic examination of the gastric residuum was requested, and on October 12 an attempt was made to pass a 12 French Rehfuess tube into the stomach under fluoroscopic observation. Various maneuvers were tried with the patient in both the erect and horizontal positions, but after 45 minutes the tip of the tube descended to approximately 3 to 4 cm. above the diaphragmatic hiatus. This level was estimated to be at the location where the esophagus courses toward the left across the vertebral column. Fifteen to 20 cc. of viscid material were removed by syringe from the esophagus. No lavage was used as it was feared fluid might be injected into the bronchial tree since the tube contained additional perforations.

On October 13, 1948, roentgenograms of the esophagus disclosed "a fairly constant radiolucent defect just above the level of the diaphragm, which changed in configuration. Proximal to this defect the esophageal lumen was narrowed to $\frac{1}{2}$ cm.; mucosal folds converged into this area."

Because this was an inadequate study it was repeated three days later with the following report: "A narrowing, 3 cm. long, was seen in the distal third of the esophagus, the lower margin of which was about 1 or 2 cm. proximal to the esophageal opening in the diaphragm. The constricted area did not distend to a normal caliber. The posterior margin of this region was irregular in contour, the mucosal pattern of which was moderately distorted." From a roentgenologic point of view, it was thought a malignant neoplasm involved the distal third of the esophagus. See Fig. 1.

On October 18, 1948, an esophagoscopy was performed. "In the region of the hiatal orifice of the esophagus, the lumen is very definitely reduced and the surface appears irregular although the mucous membrane is intact. The left wall of the esophagus appears to show more bulging of the submucosal thickening. Because of the constriction of the lumen, it was impossible to advance into the cardia of the stomach for direct inspection of this area. Since there was no definite fungation present we could only scrape off a little tissue from the surface for histologic examination. We were able, however, to get an ample specimen of bloody secretion from beyond the point of constriction, which was sent to the laboratory for tumor cell study." The esophagoscopist thought the lesion arose from the cardia of the stomach and infiltrated the wall of the esophagus.

The pathological report of the secretion from the esophagus was that the smear showed no cells on which one could focus, and that the tissue showed no evidence of carcinoma.

On October 21, 1948, a resection of the carcinoma of the esophagus and an esophago-gastrostomy were performed. The left pleural cavity was entered and the diaphragm was divided so that the stomach could be mobilized. Mobilization of the esophagus was carried out by splitting the parietal pleura over the esophagus which was then dissected free for a distance of $3\frac{1}{2}$ inches above the upper level of the gross lesion located approximately 5 cm. above the esophago-cardiac junction. The esoph-

agus was transected at the esophago-cardiac junction; the fundus of the stomach was pulled into the chest and anastomosed to the posterior wall of the esophagus. After the anastomosis was completed it was rotated through 180° and fixed with



FIG. 1. Slight deformity at lower end of esophagus demonstrated by X-ray.

stay sutures. The pleura was sutured together over the esophago-gastric anastomosis, the diaphragm was closed and the stomach was fastened to the lateral thoracic cage. The chest wall was closed and the lung was reexpanded by means of a catheter. Following an uneventful recovery, the patient was discharged on 11/7/48.

Cytology of the Esophageal Sediment

Fifteen smears of esophageal sediment stained by the technique of Papanicolaou¹ were examined. Diffuse sheets of squamous epithelium, blue to faint pink in color, were very plentiful. The nuclei of these cells were normal in size and ovoid in shape. Here and there a few columnar cells were seen in the smears.

Interspersed among the sheets of squamous epithelium were large atypical cells, the cytoplasm of which was abundant, and stained grey to a faint blue color. See Figures 2 and 3. The shape of the cells was polyhedral or ovoid or



FIG. 2. Group of malignant cells characterized by large nuclei with prominent nucleoli. These cells were obtained by aspiration of the esophagus and stained after the method of Papanicolaou.

triangular; "tadpole" shaped cells were frequently seen. The nuclei were demarcated by a hyperchromatic nuclear membrane; the nucleoli were prominent. A few of these atypical cells contained two or three nuclei.

These smears were classified as Papanicolaou Class IV (malignant cells noted). It is believed these malignant cells arose from squamous epithelium rather than from gastric epithelium because of these characteristics:

1. The increased size of the atypical cell.
2. The presence of "tadpole" shaped cells.
3. The abundant grey staining cytoplasm.
4. Some degree of keratinization in several atypical cells.

Gross Examination

The surgical specimen consisted of a portion of resected esophagus (lower one-third) which measured 7 cm. in length and 5 cm. in circumference. The mucosa appeared normal throughout except in the aboral region which contained an area of ulceration. The ulcer measured 1.5 cm. in length, 0.5 cm. in width and 0.5 cm. in depth. The base of the ulceration showed necrosis and hemorrhage, and the edges were rounded and indurated. The wall of the esophagus in the region of the ulceration appeared pearl grey, was firm to touch, and measured 0.8 cm. in thickness; elsewhere it was 0.5 cm.

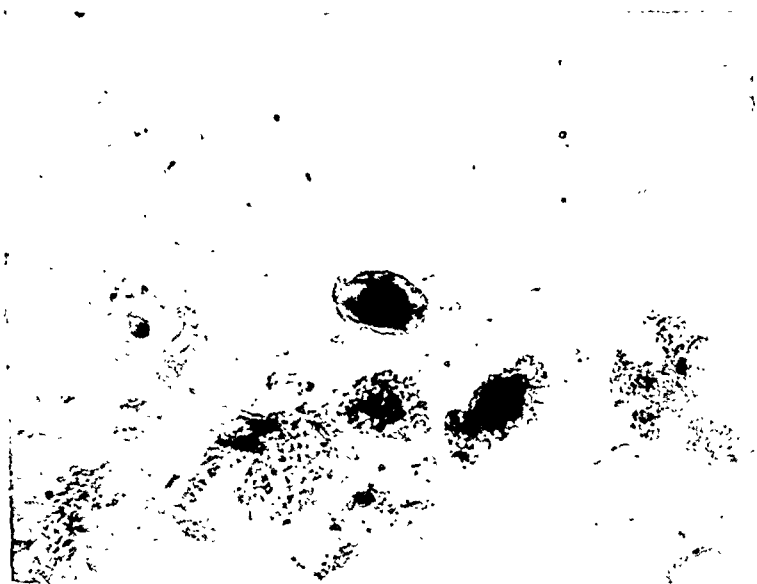


FIG. 3. Single malignant cell with a normal squamous cell adjacent to it. This cell is identical with the cells shown in Figure 5.

Microscopic Examination

Microscopic examination of the lesion revealed an intra-epidermal carcinoma. The submucosal, muscular and adventitial coats were free of invasion by neoplastic cells. These features are demonstrated in Figures 4 and 5. The pathologic report was "chronic ulcer with fibrosis and in one area the epithelial covering showed abnormal cells similar to Bowen's disease.

SUMMARY

Since we began examining the cytology of gastric sediment in patients with gastrointestinal symptoms, we encountered one individual in whom the tip of



FIG. 4. Section through the edge of the ulcer. Note the line of demarcation between the malignant and normal epithelium shown in the upper right hand corner. The malignant process is confined to the mucosa; the submucosa shows only a chronic inflammatory reaction.

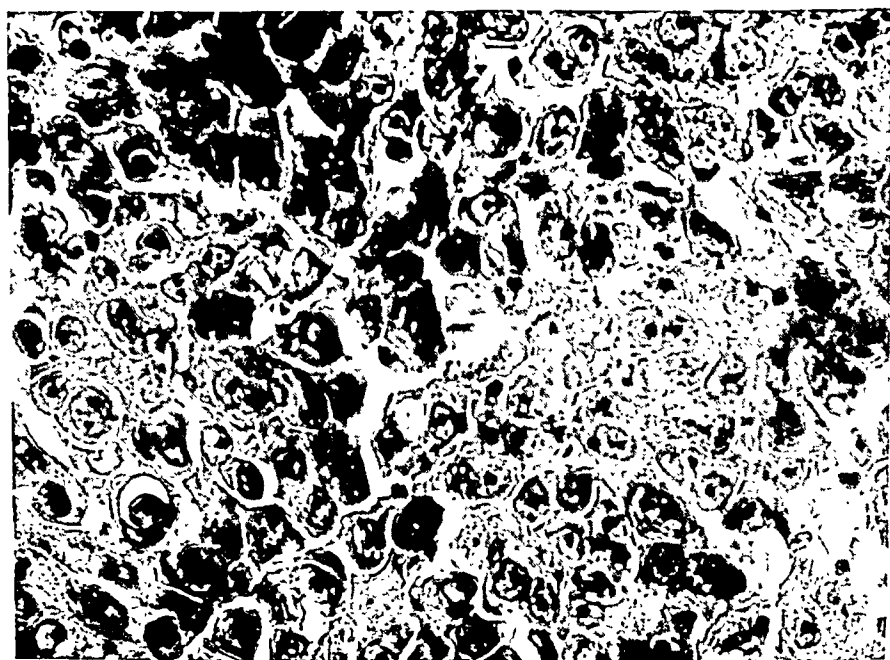


FIG. 5. High power magnification of malignant epithelium shown in Figure 4. Note the irregularity of the shape, size and staining qualities of the malignant cells; also note loss of polarity.

a Rehfuess tube did not pass through an area of narrowing in the lower third of the esophagus. Cytologic examination of material aspirated from the esophagus

disclosed malignant cells. The increased size of the atypical cells, the presence of "tadpole" shaped cells, the abundant grey staining cytoplasm and the presence of keratinization in some of the atypical cells suggested that a neoplasm arose from squamous epithelium.

A week later, at esophagoscopy a narrowing of the esophagus was encountered at its hiatal orifice. It was not possible to traverse this narrowed region to inspect the tissue beyond, and the esophagoscopist commented, "There is definite suspicion that the lesion may arise from the cardia of the stomach itself, which is infiltrating the wall of the esophagus. . . ." The mucosa appeared normal but a bulging of the submucosal thickening was seen. A biopsy of this region showed no evidence of carcinoma, and secretions from the esophagus, removed at the time of esophagoscopy, were uninformative cytologically.

At the time of transthoracic esophagectomy, the upper level of the gross lesion was estimated to be 5 cm. proximal to the esophagocardiac junction.

Microscopic examination of the surgical specimen revealed an intraepidermal carcinoma. This represents a carcinoma in situ.

CONCLUSIONS

1. Esophagoscopy was performed on a patient with carcinoma in situ of the esophagus. Although the esophagoscopist thought a lesion was arising from the stomach, biopsy and secretions obtained at the time of esophagoscopy were reported negative for the presence of malignant cells. However, when the patient was intubated a few days earlier with a Reh fuss tube, cytologic examination of the esophageal contents demonstrated malignant cells, the identity of which was verified by the microscopic appearance of the surgical specimen.

2. Intubation of the esophagus is suggested as an adjunct to roentgenologic and endoscopic examinations in suspected lesions of the esophagus. When we have not been able to obtain material from the esophagus, we have instilled physiological saline through the tube or permitted the patient to sip small quantities of saline; aspiration generally contains a sufficient amount of sediment for study.

ACKNOWLEDGMENTS

The authors wish to thank Dr. H. L. Bockus who stimulated our interest in cytologic examination; Dr. L. Kraeer Ferguson who permitted us to study the patient; Dr. Arthur Finkelstein for the use of roentgenograms; and Dr. T. A. Johnson for his criticisms and suggestions during the preparation of this manuscript.

The dyes were provided by Ortho Pharmaceutical Corporation, Raritan, New Jersey.

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HODGKIN'S DISEASE OF THE STOMACH

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Lymphomatous tumors of the stomach, often called gastric sarcomata, are not too rare. Ewing¹ found gastric sarcomata to comprise 1% of gastric neoplasms, while Marshall and Arnoff² recently reported an incidence of 3.2% in 464 patients operated upon for gastric tumors at the Lahey Clinic. Phillips³ has stated that these tumors constituted 6.5% of gastric neoplasms in patients under 30 years of age undergoing surgery at the Mayo Clinic.

The lymphomata have been sub-divided as follows: 1. Hodgkin's disease^{1,4}. 2. Lymphosarcoma⁵. 3. Reticulum cell sarcoma^{6,7,8}. In lymphosarcoma isolated gastric lesions are rare. Most commonly the gastric pathology is part of a generalized lymphosarcomatosis. Fever, splenomegaly, and anorexia are present, but rarely cachexia, anemia or occult blood in the stools. In the third group, reticulum cell sarcoma, a preoperative differential diagnosis cannot usually be made from the other lymphomatous tumors of the stomach.

However, Hodgkin's disease confined to the stomach is relatively rare. The first case of Hodgkin's disease of the stomach was reported in 1913. Rafsky and Krieger⁹ stated that the chief presenting complaint is epigastric pain, found in 75% of the cases and that the pain resembled that of peptic ulcer in half the cases. It occurs mostly in young males. Bassler and Peters¹⁰ reported an average age of 38.5 years, with three-fourths of the cases occurring in males. Madding¹¹, who analyzed six cases in men between 38 and 62 years found the average length of symptoms was nineteen months. These cases failed to show splenomegaly, lymphadenopathy, pyrexia, or anemia to any degree. The presenting complaints were weight loss and epigastric pain. Gall and Mallory⁴ described the pathological lesion as polycellular, the pathognomonic cell being the multilobed stem cell (Reed-Sternberg cell). These cells were sometimes mononucleated. There was abundant cytoplasm in the cells, and each nucleus contained a single vesiculated nucleolus. Mitosis was frequently seen.

In differentiating gastric carcinoma from Hodgkin's disease of the stomach the following points are significant. In carcinoma there is usually marked weight loss, occult blood is found in the stools, fever is rarely present, there is severe anemia, and most commonly there is achlorhydria. The lack of pain until late in carcinoma is very significant, being much different from the early complaint of pain in Hodgkin's disease. There is no response to irradiation. The evaluation of the duration of symptoms, appetite changes and x-ray diagnosis are not conclusive.

The case report which follows illustrates how a new symptom arising in a

patient under treatment for a chronic disease may be overlooked, or attributed to the chronic disease without considering it due to additional new pathology. This patient had a severe pulmonary complaint which might have completely masked a separate disease complex. It is also significant in adding an additional case of Hodgkin's disease, confined to the stomach, to the literature.

CASE REPORT

F. D., a 64 year old Italian shoemaker, was first seen on November 18, 1947, with the complaint of loss of appetite for the past six months. He stated that in 1932, he had a severe attack of bilateral lobar pneumonia from which he made an uneventful recovery. In 1942, he had a second severe attack of bilateral lobar pneumonia, after which a chronic productive cough persisted, with expectoration of one-half a cup of yellowish thick sputum daily. He also experienced dyspnea and audible wheezing on many occasions. In 1946, an examination revealed extensive bilateral pulmonary fibrosis which was non-specific in nature. Repeated sputum cultures and smears failed to reveal tubercle bacilli or fungi. No cavities were demonstrated by x-ray. Administration of intramuscular and aerosol penicillin and streptomycin did not ameliorate the cough, expectoration, and dyspnea.

In June 1947, the patient first noticed anorexia. He developed a special aversion to meats, and began to lose weight. There were no other gastrointestinal symptoms. He was treated elsewhere with various tonics, vitamin products, and antispasmodics without relief.

When seen in November 1947, he still complained of anorexia and weight loss. The cough, expectoration, and dyspnea had persisted. He had noticed a slight evening temperature elevation for the preceding two weeks.

On physical examination emaciation was noticed and inspiratory and expiratory moist rales were heard over both lungs anteriorly and posteriorly. Bilateral indirect inguinal hernias were present. Abdominal and rectal examinations were negative; the spleen and liver were not palpable. No lymphadenopathy was found. Blood pressure was 120/80; temperature 101 degrees, pulse 80, regular; respirations 18, and shallow.

Laboratory findings: Blood Count: Hemoglobin 79%, RBC 4,510,000, WBC 11,450, Lymphocytes 21%, Polymorphonuclears 74%, Eosinophiles 3%, Monocytes 2%. The urine was normal. Stool examination was negative for ova and parasites, no RBC, few WBC. Gastric analysis revealed no free hydrochloric acid in the stomach.

Fluoroscopic Studies: The heart contours were normal in all views. There was diffuse mottling of both lung fields consistent with chronic pulmonary fibrosis. The costophrenic sinuses were clear; diaphragmatic excursions were normal. Examination with barium revealed a normal esophagus. As the barium flowed over the greater curvature of the stomach there appeared to be a smooth filling defect at the incisura about the size of a lemon. The mucosa was intact. The pyloric antrum and duodenal bulb were normal. A presumptive diagnosis of tumor of the stomach, possibly of mesenchymal origin was made.

The patient was admitted to the Presbyterian Hospital on November 24, 1947 where gastrointestinal x-rays confirmed the fluoroscopic findings of gastric tumor. The patient was prepared for surgery. On December 5, 1947 laparotomy was performed. On exploration a tumor was felt along the greater curvature of the stomach. The liver was found to be normal; no additional abdominal pathology was found. A subtotal gastrectomy was performed. The patient made an uneventful recovery, and was discharged on December 15, 1947.

Tissue Examination

Gross examination: A part of the stomach measuring 10 x 5 x 5 cm. was received. On section there is a bulky tumor 5 x 4 x 2 cm. situated on the greater curvature and bulging into the lumen. The mucous surface of the tumor is smooth not ulcerating. The adjacent omental nodes are swollen, rather soft and discolored, the largest being 2 cm. in diameter. The cut surface of the gastric tumor is greyish in color appearing similar to the omental nodes.

Histological examination: The tumor is composed of cells containing large hyperchromatic nuclei, many excentrically located. There are a number of mitotic figures. These cells are separated by a scant loose reticulum. There are rare large cells containing giant nuclei resembling Reed-Sternberg cells. The growth is located mainly in the submucosa which it replaces. The muscularis mucosa is penetrated in places and the mucosa is invaded, where in addition to the cells described above, there are scattered eosinophiles. The mucous glands are atrophied but still present at the surface. The surface epithelium is intact in most of the extent covering the neoplastic tissue. The muscular coats are replaced by hyalinized fibrovascular tissue containing islands of neoplastic cells.

Diagnosis: Hodgkin's sarcoma of stomach.

The patient received 12 bi-weekly treatments of high voltage radiation (200R) to the spleen and deep upper abdominal structures, both anteriorly and posteriorly. After one year he has failed to gain weight, and his appetite is again poor. Hemoglobin has remained between 75-80% (Sahli). The spleen and liver are not palpable. No peripheral nodes can be felt. His chest symptoms remain unchanged. There has been no temperature elevation. He has not returned to work.

CONCLUSION

1. The types of lymphomatous tumors of the stomach have been reviewed.
2. The differential diagnosis from gastric carcinoma has been discussed.
3. A case of gastric Hodgkin's disease has been reported. It is also interesting because of it's insidious onset in a patient with symptomatic chronic pulmonary fibrosis.

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PAPILLARY ADENOMA OF DUODENUM PRODUCING OBSTRUCTION

REPORT OF ONE CASE

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Benign tumors of the duodenum are quite rare. Papillomas are classified with the adenomas and are usually of little clinical importance except for the possibility of malignant change, hemorrhage, or obstruction.

Waters¹ reported one case and discussed the roentgenologic appearance. Golden² reviewed the literature and found 17 cases of non-malignant tumors of the duodenum, adding two more case reports of his own. Balfour and Henderson³ reported six cases in one of which definite obstruction was present. Shaw⁴ discussed polyposis of the intestine and stated that in his opinion obstruction due to a polyp was rare; while Cassidy and Macchia⁵ reported a case of polyposis of the duodenum and jejunum with malignant degeneration and intussusception. We have recently seen a large papilloma of the duodenum producing obstruction and massive hemorrhage.

CASE REPORT

B.R., male age 69, was admitted to the hospital on May 4, 1948. He stated that for the past five years he had noted intermittent epigastric burning, occurring 5 to 30 minutes after meals, relieved by milk and amphogel, and aggravated by greasy food. During the past one year, his diet had been largely confined to soup and milk. He was frequently awakened around midnight with the epigastric burning. There had been no radiation of the pain and no nausea, vomiting, tarry stool, or hematemesis previous to the present illness.

A gastrointestinal series done at another hospital on 1/6/48 revealed a cyst-like defect (Figure 1) in the duodenum. This was noted, but unfortunately the correct interpretation was not made until after the postmortem examination was performed. It is now seen that the large defect represents the papilloma and the barium leaking around the periphery of the mass outlines the tumor.

During the three days prior to admission, the patient had noted massive hematemesis, tarry stools, and weakness. There had been a steady weight loss over the past two years, but the amount was unknown. Physical examination was negative except for moderate epigastric tenderness.

Due to the massive hematemesis, it was deemed advisable not to do a gastrointestinal series. On the third hospital day the patient developed severe upper abdominal pain with rigidity, and immediate laparotomy seemed advisable. An anterior perforated duodenal ulcer was encountered. The stomach at the pyloric end was markedly adherent posteriorly so that it was impossible to retract the site of the

pathological process into the wound. Plicating the perforation was an extremely difficult task. Due to the patient's extremely poor physical condition on the operating table, very little exploration could be done. Following operation the patient did very poorly with recurrent epigastric pain, nausea, recurrent vomiting, and intermittent bleeding in spite of continuous gastric suction and, later, a milk and amphogel constant gastric drip.

On June 10, because of the persistent obstructive symptoms, an anterior gastroenterostomy was performed, but again it was found impossible to adequately explore the abdomen due to the extremely poor condition of the patient. It was necessary to place the anastomosis much higher than desired since the stomach in the antral and pyloric region could not be mobilized adequately. A posterior gastroenterostomy was out of the question. The patient expired six days later.



FIG. 1

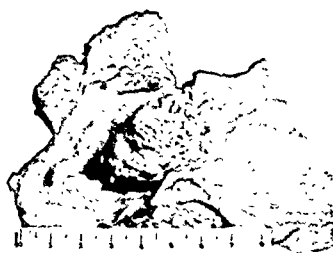


FIG. 2

At autopsy the stomach was normal. The duodenum, in its first part, was markedly adherent to the pancreas posteriorly and its dissection was difficult. The stomach and duodenum were removed and opened longitudinally. No residual evidence of duodenal ulcer could be found. A papilloma measuring 4 cm in diameter was found attached by a pedicle 1 cm long and 1 cm wide to the first portion of the duodenum approximately 1 cm below the pyloric ring (Figure 2). The polyp could be moved distally on its pedicle and appeared to be capable of producing a ball valve action completely obstructing the duodenum.

The Pathological Report is as follows (F. C. Helwig, M.D.):

Gross Pathology

Material consists of a portion of stomach and duodenum. The serosal surface of the duodenum has many delicate fibrous adhesions and is quite irregular. In one area just distal to the pylorus there is a small subserosal hemorrhage. There is a mass of

fat adherent. The serosa of the portion of stomach has a few fibrinous adhesions. The portion of stomach measures 5 cm. in length; the wall is thin and the mucosa pale and flattened. The section of duodenum is 6 cm. in length. Arising from the mucosa 1 cm. distal to the pylorus is a polyp. The stalk measures 11 mm. in its greatest diameter and 10 mm. in length. At the peak of the stalk is a sphere-shaped mass composed of frond-like structures so that it resembles a small cauliflower. The separate arborizations can be spread down to the head of the stalk and there is no firm mass of tissue present. The mucosa of the duodenum is flat, and the entire duodenal wall thinned.

Histologic Pathology

Microscopic examination shows a papillary tumor made up of long glands lined by tall columnar epithelium with vacuolated acidophilic cytoplasm. The stroma is of loose connective tissue containing large numbers of lymphocytes. At the base many glands typical for those of the duodenum are seen. Many of the glands are dilated and contain strands of mucoid material as well as desquamated cells. The stroma-epithelial ratio varies from one area to another.

Diagnosis

On the basis of uniform character of the epithelium, a diagnosis of benign epithelial polyp of the duodenum was made.

Due to the rarity of a benign tumor of the duodenum sufficiently large to produce obstructive manifestations, it was felt that this case report might be of interest.

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Editorials

THE DANGEROUS TOXICITY OF THIOCYANATES

In view of the fact that many physicians today are giving thiocyanates, often without good follow-up control, the recent paper by Gorman, Messinger and Herman (May, 1949, *Annals of Internal Medicine*) is well worth reading. They point out that there have been a number of cases of fatal poisoning with the drug, and what is most disturbing is that in a number of these, the total dosage was low. In 8 cases the amounts given were 3.3, 8, 9, 12, 15, 18 and 25 gm., respectively.

Barker, who introduced the method for determining thiocyanate in the blood, felt in 1939 that no cases of severe intoxication are likely to appear at a blood level below 20 mg. per 100 cc. From their experience with some 300 cases, Gorman, Messinger and Herman thought the optimal blood titer was between 8 and 14 mg. per 100 cc. Massie, Etheridge and O'Hare thought it should be from 5 to 7 mg. per 100 cc. The sad feature now is that in several cases, death has resulted when the blood level was within the supposedly safe range. In 3 fatal cases, the titer in the blood was 3.3, 4.2 and 7.0 mg. per 100 cc.

The usual symptoms of toxicity at the beginning are dermatitis, psychotic manifestations, enlargement of the thyroid, thrombophlebitis and convulsive twitchings. Sometimes coryza-like symptoms appear. There may be pruritus, a maculopapular eruption and exfoliative dermatitis. There may be edema of the glottis and larynx. In most of the fatal cases, there have been confusion, hallucinations, delusions and psychomotor agitation. Such symptoms give a bad prognostic outlook.

In view of these dangerous possibilities, it certainly would be unwise to give the drug to patients who are not going to be watched. It would be bad enough to use such a dangerous drug if it were certain that the blood pressure would come down and life would be prolonged. Unfortunately, even when the pressure comes down, there is as yet little evidence that life will be prolonged or made more comfortable. That is the difficulty with all the treatments for hypertension. We physicians and the patients all want the pressure reduced, but will that do any good? Commonly, it does not.

[W. C. A.]

PTEROYLGLUTAMIC ACIDS AND RELATED COMPOUNDS

Recently it has become clear that several vitamins or vitamin-like factors, such as folic acid and the L. casei factor, owe their action to pteroylglutamic

acid or related compounds. The subject is of such great interest to all students of nutrition that we take pleasure here in calling attention to a splendid review by T. H. Jukes and E. L. R. Stokstad, of the Lederle Laboratories Division of the American Cyanamid Company. The article is in the January, 1948 number of *Physiological Reviews* and covers 56 pages. There is a bibliography of 306 titles.

Spies, using the new vitamin, has reported wonderful results in the treatment of the glossitis of pellagra. Much study is being done now on the way in which the new drug acts or does not act on various types of anemias and blood diseases.

[W. C. A.]

Comment

THE RUBBER FINGER TIP OF THE GASTROSCOPE

A WARNING

Lately gastroscopes without rubber finger tip have been described, constructed and marketed. Every method which works inside the human body has some inherent danger; it is essential to reduce this danger as much as possible, to make the method as safe as possible, even if absolute safety cannot be obtained. The construction mentioned cannot be considered sufficiently safe, and it seems appropriate to recall some historical facts which had led to the universal adoption of the protective rubber finger.

The rubber finger attached to the tip of the gastroscope has a dual purpose. (1) it prevents the production of hypopharyngeal lesions; (2) it protects the stomach wall from perforation.

(1) The constrictor muscle of the pharynx may be open, especially if the patient makes a swallowing movement; in this case any kind of instrument can be introduced into the esophagus without danger, but the muscle often is closed. If it is not spastically closed, its walls can be disengaged by any obturator-like instrument, by a finger-less lamp as well as by the standard rubber finger. The real danger looms when the constrictor muscle is spastically closed. Lesions will then be avoided with open tubes, if the examiner does not proceed without seeing the lumen of the esophagus. But even in the most expert hands, they can occur. The rubber finger will bend over the contracted space and will distribute the pressure of the instrument over a rather large mucosal surface. A metal lamp without rubber finger, however, hits only one point of the very vulnerable pharyngeal mucosa and has a tendency to traumatize it.

In 1923, after the publication of the rigid Schindler gastroscope, the author was invited by Professor Sauerbruch to demonstrate the instrument in his hospital. I declined this invitation because Professor Sauerbruch had invited simultaneously Dr. W. Sternberg from Berlin for a similar demonstration. Sternberg had published his own gastroscopic construction a short time before. As explanation for my refusal I pointed out that I considered Sternberg's instrument as unsafe, because it did not have the protective rubber finger. I did not want, I said, to see my instrument discredited by simultaneous demonstration with a dangerous instrument. I asked Professor Sauerbruch's permission to demonstrate my gastroscope independently. This request was granted, and the demonstration was successful. Sternberg demonstrated his instrument some time later, and caused a lesion of the pharynx at the very first demonstration. The patient succumbed to mediastinitis. Sauerbruch pub-

lished this accident at once, and it was a terrible blow for the new method. At first it looked as if it would be a mortal one, and very patient work was required to save gastroscopy.

(2) For some time the instrument maker G. Wolf, producer of the first flexible gastroscope, had followed Henning's suggestion and had replaced the rubber finger tip by a rubber sponge ball. I was forced to use this tip over my protest. Wolf discarded this tip only after I had produced three perforations of the stomach within a series of only 50 examinations. Ruptures and perforations of the stomach were almost unknown in the period of 10 years in which my rigid instrument with rubber finger was the standard instrument (Hübner). We now know that they may occur even with the rubber finger, without demonstrable reason, but they are exceedingly rare. In fact, during 6000 gastroscopies with the flexible gastroscope with the rubber finger, done after the mentioned 3 lesions, I have seen one rupture of the stomach and one perforation of the stomach, both non-fatal. It follows that lesions of the stomach occur in 0.03%, if the rubber finger is used, but that they occur in as much as 3%, if the rubber finger is not used. After the mentioned 3 perforations with the rubber sponge tip had happened, Renshaw and I tried to find experimentally the difference between the various types of gastroscopic tips. We stretched a dog stomach tightly in a frame and placed it at an angle of thirty degrees to the horizontal. The gastroscope, attached to a metal upright and exactly counterbalanced, was gently placed in contact with the uppermost part of the membrane. Water was slowly added to one of the balancing bottles in order to increase gradually the pressure of the instrument on the surface of the stomach. There was a relatively constant weight which caused the rubber finger to suddenly slide the full length. Once movement was initiated, the tip slid easily and rapidly. With the sponge tip, however, it required approximately 100 grams more to initiate sliding which was jerky. When the stomach was suspended loosely the finger tip passed easily over the mucosa, whereas the sponge tip "skidded" along the surface. The mucosa behind the advancing sponge was stretched tightly, while folds of tissue were piled up in front of the tip. Many times there was so much tissue piled up in front of the sponge tip that it was impossible to pass over it. In these instances the sponge tip pushed out a deep pouch and finally the instrument "buckled", but the tip did not turn upward and slip out of the pouch. It was found that the long rubber finger directs the instrument in the line of least resistance and initiates bending of the flexible portion, thereby distributing pressure over a rather large area of the posterior wall. Henning later recommended a smooth ball tip, but even this cannot deflect the instrument or facilitate its bending. The same is true of metal tips entirely unprotected as being constructed again. With these devices the pressure of the advancing gastroscope is not distributed, but localized to a small point beneath the tip.

Young gastroscopists today cannot imagine under what struggles gastroscopy was developed to its present status. I believe that a serious warning is in order. Mishaps caused by a faultily constructed instrument may discredit an important method.

RUDOLF SCHINDLER

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SPACES OF DISSE

Since the advent of needle biopsy of the liver, considerable discussion has again arisen concerning the existence and significance of the perisinusoidal spaces. These spaces, lying between the sinusoids and the polygonal cells, are considered by some as agonal and postmortem artifacts. Others, however, consider them important lymph channels with functions that help explain some of the biochemical abnormalities found in regurgitation jaundice. In view of the interest pertaining to these spaces, one may wonder why the eponym applied to them enjoys such a wide variety of spelling. To wit:

Space of Desse, according to T. B. Mallory (*J. A. M. A.*, 134: 655, 1947) and *The American Illustrated Medical Dictionary* (Dorland), 21st edition, 1947.

Space of Dissé, according to Watson and Hoffbauer (*Ann. Int. Med.*, 25: 195, 1946).

Space of Disse, according to Bockus' *Gastroenterology*, 1946.

In 1890 an article entitled, "Ueber die Lymphbahnen der Säugetierleber" appeared in the *Archiv f. mikr. Anat.*, 36: 203-224. The author is listed as *J. Disse*, "Prosector u. Privatdocent" at Göttingen, Germany. The "J" stands for "Joseph," according to the Index Catalogue of the Library of the Surgeon-General's Office, U.S. Army, Second Series, Vol. IV, p. 430, 1899; but the Third Series of the same Catalogue gives the name as "Josef." (Vol. IV, p. 691, 1923).

Perusal of Disse's article indicates that he was far from the first to describe the spaces now carrying his name or variations thereof. He presents, in fact, a rather extensive list of previous writers discussing the pros and cons of the perisinusoidal spaces. According to Disse, the first to describe these spaces and to suspect them of being lymphatic channels was MacGillavry in 1864. Little advantage would be gained, however, by changing the name to Spaces of MacGillavry; sooner or later, one surmises, the spaces would become known as those of Macgillavry, McIllaroy, or Macgillicuddy.

F. J. INGELFINGER

Book Reviews

THE BASIC NEUROSIS Oral Regression and Psychic Masochism. *Edmund Bergler*, M.D. Grune & Stratton, Inc. New York. 1949. pp 353 Price \$5.00

As one reads a considerable portion of the psychiatric literature of today, one gets to wondering if the psychiatrist may not have been more screwy than his patient. One is reminded of what the inmates of insane asylums say, that the only way you can tell a psychiatrist from the patients is that the psychiatrist has keys to the doors.

One of the best comments on the present type of psychiatric literature was made a while ago by the New Yorker. A teacher of psychiatry at Yale had written that a man with ulcer who was taking milk every two or three hours was doing this because in infancy his mother had often denied him the breast. This had enraged him and he was now compensating! The editor of the New Yorker said "Yes, perhaps, but then again, maybe the guy just likes milk!"

So often a certain type of psychiatrist can spin the most astounding theories as to why man does a very simple and easily explained act. The other day the reviewer read an article in which it said that one of the prominent signs of beginning schizophrenia is a tendency to attach tremendous symbolism to everything. This sentence made us do a lot of wondering. Doctor Bergler admits in the preface that quite a few men, on reading this book, will wonder, but he implies that perhaps 100 years from now everyone will admit that he was right and those who now scoff will be seen to have been stupid.

This is a good book for a man to read if he wants to get an idea of how complicated human motives are now supposed to be. For instance, on opening to page 166 we read, "Everybody lives psychologically on the basis of his best defense mechanism. This unconscious defense mechanism happens to be, in oral cases, pseudo-aggressive denial of the masochistic wish to be denied. Therefore, pseudo-aggressive elements dominate both in ejaculation praecox and in aspermia. In both cases fluid is denied: in premature ejaculation the "milk" is "spilled" before it can reach the mouth (vagina)." In other words, the man ejaculated prematurely because he wants to deny the woman sperm which he thinks interests her most! According to another authority of this type, premature ejaculation means an urethral-anal wish to soil the woman.

In our childish ignorance of psychiatry we have always been impressed by the statement of many men with premature ejaculation that the only reason for it was that they were too nervous and sensitive and on edge or they had not had intercourse for some time, and hence the mechanism was on a hair trigger. On a second attempt with the mechanism less sensitive the man was all right. Instead of being angry at the woman and trying to hurt her, as psychiatrists claim, he was terribly embarrassed and humiliated over his failure to achieve pleasure himself and to give it to his partner.

One wonders why universities tolerate certain psychiatrists in their midst or why the psychiatric editors take many papers that they now take. Some day they will be very ashamed.

PAIN SYNDROMES Treatment by Paravertebral Nerve Block. *Bernard Judovich William Bates and Joseph C. Yaskin*. F. A. Davis Company, Philadelphia, 3rd edition. 1949. pp. 357.

This is a very useful book. It used to be called Segmental Neuralgia and Painful Syndromes. There is much of great interest to the gastroenterologist. It is obvious that the authors have good powers of observation and have made good use of them. This is a book that every diagnostician would do well to read carefully from cover to cover. It is so helpful to know the significance of pain in certain spots.

In chapter 13, the authors discuss their use of a distillate of the root of the pitcher plant for the relief of neuralgic pains. The analysis showed that the essential substance is an ammonium salt. Of late, they have used ammonium sulphate in addition to intracaine or procaine for therapeutic nerve block in the neuroglia. It gives a more prolonged action.

There are doubtless many people going around with pain who could be helped by a numbing injection expertly made.

THE CIBA COLLECTION OF MEDICAL ILLUSTRATIONS. A compilation of Pathological and Anatomical Paintings prepared by Frank H. Netter. Commissioned and published by Ciba Pharmaceutical Products, Inc., Summit, New Jersey, 1948, pp. 222.

This is a beautiful volume with magnificent reproductions of excellent colored illustrations showing both the normal and the diseased body.

ABSTRACTS OF CURRENT LITERATURE

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MOUTH AND ESOPHAGUS

VINSON, P. P. Diagnosis and treatment of hiatal diaphragmatic hernia. *Southern Med. J.*, 42: 176 (Mar.) 1949.

This paper is based upon a study of an unusual group of 147 patients with hiatal diaphragmatic hernia. There were included 110 cases of short esophagus with a partially thoracic stomach, 21 patients with a para-esophageal hernia, and the remaining 16 with a short esophagus with a definite cicatricial stricture at the junction of the thoracic stomach and esophagus.

Flatulence, postprandial distress, fullness in the epigastrium and "acid indigestion", all worse on lying down are common symptoms. Epigastric pain, with radiation sub-ster-nally or down one or both arms, is a frequent complaint. The pain may suggest coronary artery disease, biliary colic or cardiospasm. At other times, the pain may be dull and burning and may be mistaken for that produced by peptic ulcer. Ulceration occurring at the junction of the esophagus and the stomach is frequently diagnosed as peptic ulcer. When hematemesis is the main symptom, bleeding peptic ulcer or varices

may be suggested. Dysphagia is unusual before the age of 40 years, and characteristically is intermittent, occurring especially when meat is eaten. Sudden complete obstruction with meat is not uncommon, and esophagoscopy manipulation may be required to dislodge the foreign body. Stagnation of food probably occurs in all patients, even when dysphagia is absent.

The diagnosis is best established by roentgen examination, especially in the Trendelenburg position. Esophagoscopy is of some value in short esophagus, but is useless in para-esophageal hernia. Short esophageal type of hernia is best treated by the passage of dilating sounds over a guiding thread into the stomach. If spasm is responsible for dysphagia, passage of a #60 Fr. sound usually provides complete and permanent relief. Pain and bleeding are also usually abolished by dilatation, but digestive distress often persists. In para-esophageal hernias, when dysphagia is the only symptom, dilatation gives satisfactory relief. When other symptoms are present and the patient is in good condition, operation is necessary.

ANTHONY M. KASICH

MOHS, F. E. Chemosurgical treatment of tumors of the parotid gland. A microscopically controlled method of excision. *Ann. Surg.*, 129: 381 (Mar.) 1949.

The main objective in the treatment of tumors of the parotid gland is complete removal of the neoplasm. The second objective is preservation of the facial nerve. The author describes the application of a chemosurgical technic to 13 carcinomas and 4 benign mixed tumors of the parotid gland. The method of treatment involves tissue destruction by repeated application to the tumor of zinc chloride in a paste. This is accompanied by microscopic examination of selected bits of tissue to determine the exact extent of the lesion. The latter form of control enables the operator to remove selectively all tumor tissue, with a minimum disturbance of non-neoplastic tissue including the facial nerve.

Eleven of the patients with carcinoma were followed for a 3-year period. There was a 63.6 per cent survival rate without evidence of recurrence. It is suggested that such a time-consuming chemosurgical method is justified because it permits following and removing "silent" (grossly invisible) outgrowths from the main tumor mass under microscopic control.

LEMUEL C. MCGEE

MERENDINO, K. A., VARCO, R. L., AND WANGENSTEIN, O. H. Displacement of the esophagus into a new diaphragmatic orifice in the repair of para-esophageal and esophageal hiatus hernia. *Ann. Surg.*, 129: 185 (Feb.) 1949.

The authors describe a new technic for the surgical repair of hiatus hernia. The esophagus is displaced anteriorly, and to the left if necessary, into a new location by incising the diaphragm; the right and left crura of the diaphragm are sutured together behind the esophagus. The procedure is said to have the merit of placing "strong tissues" about the esophagus. Thirteen cases of hiatus hernia of the diaphragm repaired by this technic have been followed up for periods of 5 to 36 months. There have been no recurrences of hiatus hernia.

LEMUEL C. MCGEE

STOMACH

ROGEL, K. On linitis plastica and on sclerosing carcinoma of the stomach (carcinoma disseminatum Krompecher; carcinoma fibrosum Konjetzny). *Acta Chir. Scand.*, 97: 451 (Feb.) 1949.

The author reviews the literature dealing with benign and malignant sclerosis of the stomach. He suggests that the term, linitis plastica, be reserved for benign sclerosis of the stomach and that the malignant form be called, "fibrous disseminated carcinoma". The clinical histories and macroscopic and microscopic pictures of 14 cases of malignant sclerosis are reported.

DAVID A. DREILING

GRIMES, A. E. Retrograde intragastric intussusception of the jejunum following subtotal gastrectomy. Report of a case, apparently the second such in the literature. *Ann. Surg.*, 129: 404 (Mar.) 1949.

A 55-year old white male underwent a subtotal gastrectomy (posterior Polya-type anastomosis) for a recurrent, bleeding, chronic duodenal ulcer. Two and one-half years later, he was given a transurethral resection of the prostate gland. Before the latter operation was completed (spinal anesthesia), he became nauseated and had severe retching and vomiting. The vomiting continued following this operation. After 6 days of parenteral nutrition, an X-ray examination of the stomach showed obstruction at the gastrojejunal junction. The patient subsequently died. At autopsy it was found that there was a retrograde jejuno gastric intussusception of the efferent portion of the jejunum.

LEMUEL C. MCGEE

WEST, J. P. Total gastrectomy for carcinoma of the stomach. *Ann. Surg.*, 129: 373 (Mar.) 1949.

Among 18 patients undergoing gastrectomy for carcinoma of the stomach, there were 7 deaths, an operative mortality of 39 per cent. Six of the survivors died subsequently, 5 due to a recurrence of carcinoma and 1 of inanition without postmortem evidence of neoplastic disease. No satisfactory evidence was found for this failure in nutrition under

an adequate food intake. Of the 5 surviving patients, one has an occasional diarrhea and one has an erythrocyte count below four million. Three of four patients in whom a small amount of stomach was able to be left have enjoyed a better nutritional state than those in whom the entire stomach was removed at operation.

LEMUEL C. MCGEE

KATZ, J., DRYER, R. L., PAUL, W. D., AND ROUTH, J. I. Effect of acetyl salicylic acid on the gastric mucosa of the Shay rat. *Am. J. Dig. Dis.*, 16: 88 (Mar.) 1949.

The authors refer to previous gastroscopic studies of patients who had taken large doses of aspirin, and it is observed that these reports did not indicate that the continued taking of this drug resulted in local changes in the gastric mucosa. The effect of high doses of aspirin on the gastric mucosa was studied in a group of rats prepared by a modified Shay technic.

Thirty of 31 rats, receiving oral dilute hydrochloric acid, distilled water or normal salt solutions, showed gastric lesions 6 hours after pyloric ligation, but only 15 of 35 animals receiving 2.5 gms of aspirin showed evidence of gastric damage. The rats receiving aspirin showed a lowered rate of secretion of gastric juice and had almost no free acid in the gastric contents. Aspirin seemed to have an antisecretory effect under the experimental conditions employed. It could not be stated that the decrease in free acid and of the rate of secretion was responsible for the lessened incidence of ulceration in these rats.

HENRY TUMEN

LINDBLOM, K. Roentgen diagnosis of phlegmonous gastritis. *Acta Radiol.*, 28: 33 (Feb.) 1947.

Phlegmonous gastritis is a suppurative lesion of the stomach, involving chiefly the submucosa. It is usually diffuse and only occasionally localized (carbuncle-like). Invariably the lesion is diagnosed at necropsy, following a history of several days of epigastric pain, fever, and vomiting, peritonitis and septicemia.

Roentgen diagnosis has been identified

with narrowed lumen (thickened gastric wall) and obliterated mucosal folds. In the pre-pyloric region, narrowing causes retention of barium. Pathogenesis results from an infection from a local or distant focus, a foreign body, or as a sequel to gastric operations.

The author describes a postoperative case of a 47-year old male who, 12 days following a gastric resection for gastric ulcer, developed fever and tenderness in the left epigastrium, with local pain and nausea. Two roentgen examinations revealed typical findings. Chemotherapy resulted in complete recovery and repeat films, 3 weeks later, showed normal mucosal pattern.

A. I. FRIEDMAN

BOWEL

FICARRA, B. J. Visceral activity in small bowel perforation. *N. Y. State J. Med.*, 49: 420 (Feb.) 1949.

Animal experiments have shown that stimulation of the small intestine by mechanical or chemical means produces a contracture above the point of stimulation, and a relaxation below. This "law of the intestine" is controlled by Auerbach's plexus. The author produced rents in the small intestine of rabbits. A contraction of the intestine above the point of perforation with a relaxation below, was set up immediately. This prevented the evacuation of the intestinal contents above the site of perforation. The same process was repeated many times. After about 4 hours of constant stimulation, muscular fatigue ensued and intestinal contents spilled into the peritoneal cavity. The author believes that the same mechanism occurs in humans following nonpenetrating abdominal trauma. No physical signs are evident during the stage of active contraction. It is only after the muscle becomes fatigued that the intestinal contents escape and cause a peritonitis. Laparotomy should be performed early in suspected cases.

PHILIP LEVITSKY

JONES, F. A. AND PAULLEY, J. W. Intestinal lipodystrophy (Whipple's disease). *Lancet*, 256: 214 (Feb.) 1949.

There have been less than 25 cases of intes-

tinal lipodystrophy (Whipple's disease) described in the literature. The author's case concerned a 44-year old man whose first symptom was central abdominal colicky pain and bleeding per rectum. Diarrhea and loss of weight ensued rapidly. The abdomen became distended and pigmentation of the skin and mucous membranes was noted. No abnormality was found in the alimentary tract by X-ray. There was a secondary anemia, a histamine-fast achlorhydria, and a flat glucose tolerance curve. Blood chlorides were low. Fat balance studies showed that 78 per cent of ingested fat was absorbed as compared to 90 per cent in normal individuals. Treatment consisted of a high-protein, high-vitamin, low-fat diet, and "Doca" was given in 10 mg. daily doses, supplemented with suprarenal cortical hormone. Folic acid and crude liver were also administered. Death occurred about 1 year after onset. There was a weight loss of about 35 lbs. Autopsy revealed many peritoneal adhesions and "sugar icing" of liver and spleen. The first 2½ feet of jejunum were normal; beyond this, the small bowel was atrophic and plum colored. The lymphoid tissue in the ileum was hypertrophied. The mesenteric nodes were enlarged and firm, and on a cut surface were pale and cystic. The large bowel was normal. Microscopically, the suprarenal glands showed "pyknosis" (fuchsinophilia) of the cortical cells with depletion of lipoids; the appearance was similar to that found in starvation and deficiency states. The mesenteric gland sinuses were grossly dilated with fat. Foamy macrophages predominated, and scanty giant cells were present. There was some fibroblastic activity. The small gut showed the characteristic club-shaped villi with intracellular and extracellular fat. It is suggested that the disease may originate as a primary non-specific jejunitis.

PHILIP LEVITSEY

MAYFIELD, L. H. AND WAUGH, J. M. Sigmoidocutaneous fistulae resulting from diverticulitis of the sigmoid colon. *Ann. Surg.*, 129: 198 (Feb.) 1949.

Reports show that diverticulitis of the colon accounts for 3.2-18.4 per cent of the external fecal fistulae seen in patients. The au-

thors review 17 cases of sigmoidocutaneous fistulae following surgery occasioned by diverticulitis. The average age of this group of patients was 46.3 years; the youngest was 27 years old and the oldest 60 years. Twelve were men. Fourteen of the patients had had surgery for an abscess, and 3 had had surgery for the correction of sigmoidovesical fistulae. Diverticulitis had been manifest for an average of 2.5 years when the cutaneous fistulae developed. The symptoms of sigmoidocutaneous fistulae were the presence of the fistulae, abdominal pains, constipation, chills, and fever.

Fistulae of this type tend to close spontaneously and should be given a year of observation before surgical treatment. When surgical treatment is carried out, the diseased segment of the colon should be excised. In this group of 17 patients, such resection relieved 16 of their external fecal fistulae.

LEMUEL C. MCGEE

MCGRAW, A. B. Factors contributing to low mortality from appendectomy for acute appendicitis. *Arch. Surg.*, 58: 171 (Feb.) 1949.

The treatment of acute appendicitis remains one of the most serious and frequent problems confronting the surgeon. In a search for factors contributing to a zero mortality rate in acute appendicitis for the last 5½ years, the author reviewed the 1,411 cases of that disease encountered in the Henry Ford Hospital from January, 1938 through December, 1947. Data regarding the clinical material, type of operation used, postoperative care, complications and mortality are presented and analyzed. As a result of this analysis, he concludes that, in spite of the indisputable help of the sulfonamide and antibiotic drugs, the prime factors in the elimination of mortality in acute appendicitis are: (1) The alertness with which symptoms and signs of the disease are recognized, (2) the promptness with which the patient is brought to operation after diagnosis, and (3) the consistent use of an operative technic which is sound in conception and safe in detail for the difficult as well as for the uncomplicated case.

ALBERT CORNELL

DONHAUSER, J. L. AND ATWELL, S. Volvulus of the cecum. *Arch. Surg.*, 58: 129 (Feb.) 1949.

Volvulus of the cecum is usually considered a rare condition but, in many cases, it has masqueraded for years as chronic or recurrent appendicitis before a severe attack revealed the true diagnosis. The authors review 100 cases in the literature and report 6 new cases. From a summary based on these cases, they find torsion of the cecum may occur at any age but, in 50 per cent of the cases, it occurs in patients between the ages of 20 and 45. It occurs in men and women in an even ratio. Most patients give a history of previous attacks; the signs and symptoms usually are those of obstruction of the bowel. Considerable distention and a mass are often present. Pregnancy, previous operation, high-roughage diet, strong catharsis, dietary indiscretions and unusual exertion are some of the predisposing or precipitating factors.

The authors conclude that, for torsion to occur, there must be hypermobility of the cecum, which condition is present in 20 per cent of the population, and there must be a fixed point about which the cecum may rotate. Torsion of the cecum, particularly partial torsion, is more frequent than the reported incidence would suggest. It should be considered in cases in which there is pain on the right side together with a long history of constipation and of previous attacks of abdominal pain. If the roentgenogram of the abdomen shows the pattern of small bowel obstruction, and there is a markedly dilated loop of bowel on the right side, a diagnosis of torsion of the cecum should be considered. If the roentgenogram made after a barium enema shows the column of barium stopping in the hepatic flexure or in the ascending colon, there is further evidence of the existence of this condition

ALBERT CORNELL

GRISWOLD, M. L. AND GOODSPEED, W. K. Factors in the mortality of the ruptured appendix. *Ann. Surg.*, 129: 260 (Feb.) 1949.

This is a statistical study of the mortality from appendicitis in a general hospital located in a suburban community. Between

1931 and 1937, 15.3 per cent of all cases complicated by perforation died. The cases having no rupture of the appendix carried a mortality of less than 2 per cent during the same period. By contrast, the mortality rate from perforated appendicitis between 1942 and 1947 was 8.7 per cent, a reduction of 6.6 per cent. A review of other published series shows a similar trend. The factors, which may play a role in this improvement, are given as: (1) Sulfonamides and antibiotics; (2) improved control of fluid, electrolyte and nutritional needs; (3) improved anesthesia; (4) tube decompression of the intestinal tract; and (5) less delay in receiving medical attention and less catharsis.

The authors conclude that patients, in the late stages of perforation, do better with nonoperative therapy, and that the removal of the nonperforated gangrenous appendix carries a low mortality even though some degree of local peritonitis may be present.

LEMUEL C. MCGEE

MELCHIOR, E. Volvulus of the cecum. *Surgery*, 25: 251 (Feb.) 1949.

Abnormal motility of the cecum, due to an ileocecal mesentery commune, may permit a clockwise rotation of the cecum around the vertical axis of the ascending colon, with resulting volvulus. More rarely, the abnormal mesentery may extend to the right colon with rotation around the horizontal axis of the transverse colon. The intensity of the strangulation, rather than its duration, is responsible for the anatomic changes and the ileus. Early surgical intervention is imperative. Previously, the accepted method of treatment was derotation and cecostomy with or without cecopexy. The mortality rate was over 50 per cent.

Six cases of volvulus of the cecum are presented with one mortality. Primary resection of the cecum with termino-ileocolostomy was chosen as the procedure of choice because: (1) The secondary dilatation of the terminal ileum allows a rapid and simple end-to-end anastomosis to be made, without the delay of mobilizing the ascending colon; (2) cecostomy and secondary closure are avoided; and (3) the risk of recurrence is eliminated. In one of the cases, cecal gangrene and peritonitis had occurred. A portion

of the good results in this case was attributed to the use of emetine which, the author states, is very effective against non-specific septic infections including those caused by penicillin-resistant organisms, particularly *B. coli*. In the one death, the poor condition of the patient made extensive surgery impossible. Derotation and enterostomy were performed with death at the end of the operation.

MARCEL PATTERSON

LIVER AND GALL BLADDER

WAHL, P. N. Diet and cirrhosis of the liver. *Arch. Path.*, 47: 119 (Feb.) 1949.

Stimulated by the frequent occurrence of adult and infantile cirrhosis among poorly nourished Indian peoples, the author undertook a comprehensive study of the relation of diet to cirrhosis. He reports an experimental study of the effect of a high-carbohydrate, low-protein diet on the liver in rats. The diet resembled the natural diet of the orthodox Hindus. Two groups of rats were studied: (1) infants (50 gm.) and (2) adults (100 gm.).

Rats of neither group showed changes characteristic of portal cirrhosis. Changes observed varied with survival time of the animals. The infants survived up to 77 days; the earliest death in the adults was at 100 days. In the livers of the infants, areas of completely dead parenchymatous cells alternated with areas of normal parenchyma. Special stains showed no appreciable increase in fibrous tissue, but quantitative determination of collagen revealed an increase varying from 0.5 to 0.8 per cent—the upper limit of normal being 0.4 per cent. The livers of the older animals were diffusely infiltrated with fat. In those animals surviving longest, increasing condensation of periportal and perilobular reticulum was found.

The paper includes a review of the world literature dealing with experimental production of cirrhosis in animals, and a less complete survey of the literature of the geographic distribution of human cirrhosis and the relation of alcohol diet and infection to human cirrhosis.

GEORGE A. BOYLSTON

WIRTS, C. W. The clinical and laboratory use of bromsulphalein. *Rev. Gastroenterol.*, 16: 125 (Feb.) 1949.

Although the exact method of the removal of bromsulphalein from the body has not been definitely established, the use of the dye in a study of liver function has been of practical clinical value. It is likely that bromsulphalein is excreted exclusively by the liver. Two mechanisms are proposed for this process: (1) Rapid removal of the dye from the blood by the Kupffer cells of the liver, and (2) the slow excretion into the bile by the hepatic polygonal cells. The authors propose to extend the BSP liver function test by studying, not only the rate of disappearance of the dye from the blood, but also the concentration and rate of secretion into the bile. They perform the standard BSP test on a patient with the duodenum intubated. Biliary specimens are withdrawn as well as blood samples. Twenty-five patients were tested 1–2 months following an attack of infectious hepatitis. From the study of these patients, the authors conclude that the biliary BSP test is of practical help in evaluating minimal or questionable hepatic functional impairment.

DAVID A. DREILING

CONAN, N. J., JR. The treatment of hepatic amebiasis with chloroquine. *Am. J. Med.*, 6: 309 (Mar.) 1949.

A preliminary publication has indicated that chloroquine, a highly active and less toxic compound of the 4-amino-quinoline series, possesses antiamebic activity in human infections of the liver and colon. In intestinal amebiasis, chloroquine alone has effected symptomatic and parasitologic cure in 17 of 32 cases, with follow-up periods of from 2 to 24 months.

In 7 cases of hepatic amebiasis, the objective clinical and laboratory examination revealed chills, high fever, hepatic enlargement and tenderness, diaphragmatic pleurisy, *E. histolytica* in the feces and also in the liver pus, positive amebiasis complement fixation test and bromsulphalein retention. In each instance, the hepatitis began to clear within 1–2 days after chloroquine administration. These results compared favorably

with the expected efficacy of emetine in this lesion. Chloroquine causes minor toxic manifestations characterized by nausea, pruritus and disturbed ocular accommodation. These 7 successfully treated cases of hepatic amebiasis with chloroquine are reported in detail. The drug was administered as chloroquine diphosphate with a schedule of 1 gram daily for 2 days, and $\frac{1}{2}$ gram daily thereafter for 2-3 weeks.

The combination of chloroquine with a superior intestinal amebicide should permit adequate treatment of any amebic infection; it points to a wider use of antiamebic chemotherapy as a diagnostic and therapeutic test in obscure infections of the liver and intestine.

MICHAEL W. SHUTKIN

KINSELL, L. W., WEISS, H. A., MICHAELS, G. D., SHAVER, J. S., AND BARTON, H. C., JR. The correlation of hepatic structure and function. *Am. J. Med.*, 6: 292 (Mar.) 1949.

Following 100 needle liver biopsies with histologic evaluation, an attempt was made to correlate biopsy, clinical, and biochemical findings in selected patients studied under controlled conditions. The clinical material arbitrarily chosen from a larger group, consisted of 3 acute, 1 subacute and 5 chronic cases with liver disease.

Interpretation of liver sections was based upon the following criteria: (1) Cellular infiltration, usually associated with the cephalin-cholesterol flocculation and other similar tests; (2) hepatocellular change, associated with increased serum bilirubin and brom-sulfalein retention and decreased hepatic glycogen storage; and (3) fibrosis, associated with the latter chemical tests or maybe with normal chemistry. From this study of liver biopsy sections, only gross information was obtained on the activity, extent and duration of the process. Activity is correlated histologically with phagocytic cell infiltration and with hepatocellular change. The chemical determinations, which indicate activity, are positive cephalin-cholesterol flocculation and thymol turbidity tests, and increased serum bilirubin and icterus index. Extent and duration of the hepatotoxic process are manifested histologically by he-

patocellular change and by fibrosis. These observations have only their simplicity to recommend them. There is a strong need for the reclassification of liver disease.

MICHAEL W. SHUTKIN

POPPER, H., STEIGMANN, F., MEYER, K. A., KOZOLL, D. D., AND FRANKLIN, M. Correlation of liver function and liver structure. *Am. J. Med.*, 6: 278 (Mar.) 1949.

This presentation concerns itself with a study of liver biopsies in relation to four problems: (1) Correlation of different liver function tests with various histopathologic phenomena independent of the underlying disease, (2) clinical classification of liver diseases on a morphologic basis, (3) evaluation of the practical improvement in the differential diagnosis of liver disease by the addition of liver biopsy to clinical and functional examinations, and (4) combined functional and morphologic evaluation of therapeutic procedures in liver disease. The results of a series of 6 liver function tests were correlated in each case with liver biopsy. This study includes 221 needle biopsies obtained in 154 patients, and 106 biopsies obtained during laparotomy.

Correlation between morphologic and functional findings helps in the evaluation of liver function tests and reveals that most liver function tests give positive results in diffuse parenchymal diseases whereas, in focal alterations regardless of severity, none or only a few tests indicate pathology. Based on morphologic and functional criteria, acute hepatic damage may be subdivided into viral, toxic, biliary, and purulent types. Different forms in each group were illustrated by clinical, laboratory and morphologic data. Liver biopsy improves the diagnosis of liver disease and can contribute significantly to the evaluation of therapy.

MICHAEL W. SHUTKIN

CRANDELL, W. B. Surgical therapy in jaundice. *Rev. Gastroenterol.*, 16: 142 (Feb.) 1949.

The surgical treatment of jaundice and general surgical problems in connection therewith are discussed. Consideration is given to complications before, during, and after surgery. Restoration of normal prothrombin

time before surgery, by intravenous administration of vitamin K, is emphasized. Maintenance of protein and carbohydrate metabolism is considered of importance. A powdered skim milk mixture was employed to good advantage. The physiopathologic basis of the deficiencies is presented.

Cyclopropane, ether, or spinal anesthetic is well tolerated. A warning is given, however, as to the necessity of avoiding hepatic anoxia which may be produced by shock or by an obstructed airway. A difficult but most important task is proper selection of patients for surgery. Needle biopsy of the liver is an addition to the diagnostic armamentarium.

Neoplasm is responsible for about 40 per cent of all cases of biliary obstruction. Early diagnosis, of course, is the desired aim. Palliative surgery may be necessary. Chordotomy and external or internal drainage for the relief of intractable pain and pruritus are among the palliative surgical measures. Jaundice as a result of a benign obstruction of the common duct, as in the case of jaundice due to neoplasm, is constant and progressive. In such benign obstructions a history of cholecystectomy is obtained. Operative injury and interference with the blood supply of the common duct are described as the main etiologic factors.

L. T. ROSENTHAL

JEMERIN, E. E. Cholecystitis emphysematosa. *Surgery*, 25: 237 (Feb.) 1949.

Cholecystitis emphysematosa is an acute inflammation of the gall bladder due to gas-producing organisms, usually of the anaerobic clostridium group. There results an accumulation of radiographically demonstrable gas within the wall and lumen of the organ. The clinical picture is that of acute cholecystitis, with pericholecystitis in most untreated cases. A plain film, taken 24-48 hours after the onset, will reveal a pear-shaped gas shadow outlining a distended gall bladder. The wall appears as a darker circumferential shadow. Later, the gas may be seen to extend into the pericholecystic tissue. Usually the biliary ducts and radicals are not outlined, in contrast with internal biliary fistulae.

Seventeen cases in the literature are reviewed, with the addition of a case seen by the author. Surgical removal of the infected gall bladder is recommended. In 10 cases in which therapy could be evaluated, there was 1 death in the 3 cases treated conservatively (with chemotherapeutic agents and specific sera), and 3 deaths in the 7 operated cases. In none of the latter was dissemination of infection responsible for death. If chemotherapy will control the process, a policy of delaying surgery until the infection subsides is advised. Should there be evidence of spread beyond the confines of the gall bladder, prompt surgical intervention plus chemotherapy is recommended.

MARCEL PATTERSON

HALL, C. A. AND DRILL, V. A. Relation of fat and protein intake to fatty changes, fibrosis and necrosis of the liver. *Proc. Soc. Exp. Biol. Med.*, 70: 202 (Feb.) 1949.

Experiments were designed to determine whether dietary liver disease in rats consists of two distinct types; one with fatty change and fibrosis, produced by a diet high in fat or carbohydrate and deficient in lipotropic substances; and a second type characterized by damage from necrosis and scarring from deficiency of sulfur-containing amino acids.

Different groups of Sprague-Dawley rats were fed diets containing: (1) 16 per cent protein and 51 per cent fat; (2) 6 per cent protein and 6 per cent fat; and (3) 4 per cent protein and 6 per cent fat. Although the 3 diets used were quite different, the hepatic lesions produced appeared to be the same. Almost all of the livers were heavily infiltrated with fat. With Diet 1, a high fat diet, and Diet 2, a low fat, low protein diet, the total lipid determinations show that the actual amount of fat in the liver was the same after both diets. Fibrosis was not seen unless fat was present; fibrosis always followed fatty change. Fibrosis was progressive, but not with the type of scarring seen following an acute injury. Minor infiltrations with fat did not result in fibrosis. It appears that the fibrosis is a result of prolonged extensive hepatic fatty change by feeding a diet high in fat or by feeding a diet low in protein. Hepatic necrosis was not produced by the diets used, and deaths from acute

hepatic necrosis were not obtained with a low protein intake.

H. NECHELES

CAPPS, R. The differential diagnosis of jaundice. *Rev. Gastroenterol.*, 16: 117 (Feb.) 1949.

Differentiation of hepatocellular jaundice and extrahepatic obstruction of the biliary tract may be a difficult problem and is of utmost significance with regard to surgical indications. Hemolytic jaundice does not usually present diagnostic difficulties. The most common cause of parenchymal hepatic disease is viral hepatitis. Infectious mononucleosis, Weil's disease, brucellosis, viral pneumonia, secondary syphilis and malaria may produce a similar picture. Toxic hepatitis is associated with a history of exposure to chemicals. Cirrhosis and neoplastic disease must be considered. The clinical picture may be confused by cramplike pains in the upper part of the abdomen during the first week of jaundice. Clay colored stools may suggest obstructive jaundice. Light colored stools over a long period are present in cholangiolitic hepatitis.

Patients with viral hepatitis may give a history of exposure to homologous serum disease (plasma, serum, blood or injections) or epidemic hepatitis (contaminated water or food). Tenderness of, and often enlargement of, the liver are noted. Exercise aggravates the symptoms. Impaired hepatic function is always present in the pre-icteric phase and is marked when jaundice appears—an important point of differentiation from obstructive jaundice. Urinary bile is increased before the direct serum bilirubin level is elevated. Urinary urobilinogen is increased except during a short period of acholic stools. Serum alkaline phosphatase is only moderately increased except in cholangiolitic hepatitis. Evaluation of tests of hepatic function depends on their sensitivity and on the duration of jaundice. Needle biopsy of the liver is added to tests of hepatic function. An opaque dye injected into the gallbladder under peritoneoscopic guidance is also of diagnostic aid.

L. T. ROSENTHAL

JANKELSON, I. R. AND MILNER, L. R. Medical therapy in jaundice. *Rev. Gastroenterol.*, 16: 130 (Feb.) 1949.

Proper classification of jaundice is a prerequisite of therapy. The medical treatment of prehepatic, hepatocellular and posthepatic jaundice is discussed. Prehepatic jaundice, hemolysis being the underlying cause, does not require hepatic management. Classification may not be possible at first without adequate studies of hepatic function.

Treatment of patients with unclassified jaundice and of those with known hepatocellular jaundice is similar. Food intake should be adequate; if necessary, increased amounts of protein and carbohydrates are given. Oral feeding is preferred, but may be supplemented by intravenous amino acids and albumin. Reduction of fats in the diet is not considered essential. Vitamins, especially vitamin K, are administered parenterally. Fluid intake should be at least 2,000 cc. unless edema is present. Bed rest is essential for patients with viral hepatitis until hepatic tenderness has subsided and tolerance to exercise is favorable.

Epidemic hepatitis should be treated under precautions of isolation similar to those for typhoid fever. Patients with homologous serum hepatitis need not be isolated. The prophylactic administration of gamma globulin is discussed. Arsenical jaundice is treated with sodium dehydrocholate or BAL. Amebic hepatitis responds to antiamebic therapy. Hepatitis in Weil's disease may respond to penicillin. Treatment of cirrhosis is similar to that outlined above. Lipotropic agents and liver extracts are considered of questionable significance. Dietary management is of utmost importance. Preoperative treatment of posthepatic obstruction consists of restoration of normal electrolyte, protein and vitamin balance. Postoperatively, large amounts of bile may be lost through drainage and may require replacement. Prothrombin values should be maintained.

L. T. ROSENTHAL

PANCREAS

POPPER, H. L. Consequences of section of the pancreatic duct. *Surg. Gyn. Obs.*, 88: 254 (Feb.) 1949.

An experimental study of the immediate consequences of cutting the pancreatic duct and leaving it open was conducted. Fifty healthy mongrel dogs of both sexes were divided into 2 series: Those in which the pancreatic duct was transected between the pancreas and duodenum, and those in which the pancreatic duct was slit open. From the experiments, the author suggests that the following measures should be considered for clinical trial: (1) Attachment of the omentum to the ligated stump, if a pancreatic duct is transected, and if implantation into the gastrointestinal tract is not feasible; (2) attachment of the omentum, in injuries to the glandular tissue of the pancreas, regardless of whether the lesion of the pancreas has been sutured or not; (3) prolongation of routine period of starvation to depress pancreatic secretion, in cases of surgery of the pancreas or when the gland is injured in the surgical procedure; and (4) maintenance of minimal external pancreatic secretion and avoidance of humoral as well as vagal stimulation of the pancreas after operation on, and injuries to, the pancreas.

FRANCIS D. MURPHY

MEYER, K. A., SHERIDAN, A. I., AND MURPHY, R. F. Pseudocysts of the pancreas. Report of 31 cases. Surg., Gyn. Obs., 88: 219 (Feb.) 1949.

Thirty-one cases of pseudocysts of the pancreas seen at the Cook County Hospital are reported. The etiological factors were: History of trauma, 16 cases; cholecystitis and pancreatitis, 6 cases; cholelithiasis and chronic cholelithiasis, 3 cases; and acute pancreatitis, 2 cases. In this series, the amount of fluid contained in the cyst varied from 15 cc. to 7,000 cc. X-ray films were of more use than laboratory tests in diagnosis of the pseudocysts. Operative procedures included marsupialization, cystocholecystostomy, cystojejunostomy, and complete excision. Marsupialization was considered the safest and most expedient procedure in these cases. Average period of drainage from cysts, following marsupialization, was 7.2 weeks; there was no instance of the development of a persistent fistula.

FRANCIS D. MURPHY

ANEMIAS

LADENSON, R. P., SCHWARTZ, S. O., AND IVY, A. C. Incidence of the blood groups and the secretor factor in patients with pernicious anemia and stomach carcinoma. Am. J. Med. Sci., 217: 194 (Feb.) 1949.

The authors determined the blood grouping of 160 patients with pernicious anemia and of 15 with gastric carcinoma (5 of whom were also in the pernicious anemia group). The saliva of the subjects was examined for the presence of blood group-specific substances. It was found that pernicious anemia was related to neither a particular blood group nor to Rh negativeness. Furthermore, these patients secreted group-specific substances in their saliva in the same proportion as normal individuals. The ratio of secretors and nonsecretors was approximately the same in subjects showing gastric atrophy as it was in those who had a normal gastric mucosa. The presence of gastric carcinoma did not appear to be associated with a specific blood group or to a change in the secretor trait.

LEMUEL C. MCGEE

HALL, B. E., MORGAN, E. H., AND CAMPBELL, D. C. Oral administration of vitamin B₁₂ in pernicious anemia. I. Presence of intrinsic factor in Berkefeld-filtered pooled human gastric juice: Preliminary report. Proc. Staff Meet. Mayo Clinic, 24: 99 (Feb.) 1949.

Parenterally, 1 microgram of vitamin B₁₂ appears to be equivalent to 1 U.S.P. unit of liver extract. However, oral vitamin B₁₂ is ineffective, in contrast with extracts of liver or stomach mucosa, in producing a hematopoietic response, unless gastric juice of human beings is given simultaneously within a period of 2 hours following the ingestion of this vitamin. Castle and associates showed that an interval of 12 hours between the ingestion of B₁₂ and the gastric juice resulted in no hematopoietic response. The present study confirms these results and also shows that intrinsic factor is present in human gastric juice through a Berkefeld filter.

Gastric juice was obtained from patients having duodenal ulcers or having functional

gastrointestinal disturbances, whose gastric juice had a free acidity of at least 30 units. The gastric juice was adjusted to pH 7.0-7.5, after passing through a Berkefeld filter. Four patients with pernicious anemia in severe relapse were studied. Vitamin B₁₂ and gastric juice were mixed within one-half hour of administration. When given alone, 25-35 micrograms of B₁₂ per week failed to produce any hematopoietic response; also 150 cc. of gastric juice given daily for 6 days elicited no response. However, 5 micrograms of B₁₂ administered daily together with 150 cc. of gastric juice resulted in a good response with a reticulocyte peak of 31.7 per cent on the 10th day. The minimal daily amount of gastric juice, required to potentiate an optimal hematopoietic response from 5 micrograms of vitamin B₁₂ administered orally to patients with pernicious anemia, is at least 25 cc.

FRANK NEUWELT

ULCER

HALE, E. H. AND GROSSMAN, M. I. The resistance of recently healed excisional ulcer of the stomach to histamine-induced ulcer. *J. Lab. Clin. Med.*, 34: 228 (Feb.) 1949.

The authors produced surgical excisional ulcers on the lesser curvature of the gastric mucosa of dogs. They found that healed ulcers did not break down and reulcerate when a suspension of histamine-in-beeswax was given 3 weeks after the ulcer was originally produced. These studies suggested that the tissue of the healed ulcer was more resistant than normal tissue. Should the findings of this study be applicable to human peptic ulcer, they would have important implications for therapy.

EDGAR WAYBURN

WYATT, J. P. AND KHOO, P. N. Ulcers of the upper part of the gastrointestinal tract associated with acute damage of the brain. *Arch. Path.*, 47: 110 (Feb.) 1949.

The authors present clinical and pathologic summaries of 4 cases of acute upper gastrointestinal lesions found at autopsy in a series of 210 cases of fatal brain injuries. The first patient (dead 3½ days after extensive traumatic skull fracture with subdural hema-

toma and hypothalamic damage) exhibited 4 shallow ulcers at the pylorus and on the lesser curvature of the stomach. The second patient (dead 5 days after spontaneous intracerebral hemorrhage) had 2 superficial ulcers at the pylorus and extensive esophageal softening and perforation. The third patient (dead 5 days after traumatic subdural hemorrhage and cerebral lacerations) exhibited 2 small, acute duodenal ulcers. Both ulcers showed a floor of cellular debris and a zone of early fibrinoid change. The fourth patient (dead 30 hours after resuscitation following an anesthetic accident and prolonged cerebral anoxemia) exhibited thinning of the gastric wall and 5 perforations of varying size.

All of these gastrointestinal lesions showed variable degrees of lymphatic and polymorphonuclear leukocytic infiltration, interpreted as antemortem change. Possible mechanisms of production of these lesions are discussed.

GEORGE A. BOYLSTON

JAMIESON, R. A., SMITH, W. E., AND SCOTT, L. D. W. Peptic ulcer in Glasgow. A hospital survey. *Brit. Med. J.*, 4598: 298 (Feb.) 1949.

A 2-year survey of the peptic ulcer patients attending a Glasgow hospital is reported. The sex ratio was 3.5 males to 1 female. The site ratio was 7.7 duodenal ulcers to 1 gastric ulcer. There was no evidence that the ratio of duodenal to gastric ulcer was influenced in males by social status, or in females by marital status. Patients with duodenal ulcer were notably younger than individuals with gastric ulcer, and the age at onset of symptoms was also lower in duodenal ulcer. In gastric ulcer, hemorrhage was a more common complication than perforation in both sexes. In duodenal ulcer, however, there was a conspicuous sex difference; in males, perforation exceeded hemorrhage in the ratio of 1.5 to 1, whereas in females, the ratio of perforation to hemorrhage was 1 to 5. The relative preponderance of duodenal over gastric ulcer was found to be much greater in Scotland than in London.

JOSEPH B. KIRSNER

FERGUSON, L. K. AND STEVENS, L. W. The role of surgery in solving the peptic ulcer problem. *Penn. Med. J.*, 52: 487 (Feb.) 1949.

Uncomplicated gastric ulcer is a surgical problem. Because of the potential malignancy of gastric ulcers, a radical resection should be performed. The authors have never encountered a recurrent or marginal ulcer following adequate resection for gastric ulcer. The role of surgery in the treatment of perforation, obstruction, and massive hemorrhage is discussed. The individual with massive upper gastric intestinal hemorrhage should ideally be followed by the surgeon and gastroenterologist from the start. When it becomes apparent, after the initial correction of the shocked state and the institution of a medical regimen, that it is difficult or impossible to sustain an effective blood pressure, operative interference should be considered without delay.

The selection of an operative procedure for peptic ulcer should be based on certain principles of gastric physiology. Gastric resection, with removal of approximately 75 per cent of the stomach, is considered the best procedure, since it eliminates the humoral mechanism of gastric secretion and a considerable proportion of the acid-pepsin-producing zone of the stomach. The mortality rate for the procedure in large clinics now ranges from 1 to 3 per cent.

It is believed that vagotomy will find its principal use as an adjunct to other procedures for the treatment of peptic ulcer. There is no place for vagus section in the primary treatment of gastric ulcer.

CHARLES A. FLOOD

COSTELLO, C. Massive hematemesis. Analysis of 300 consecutive cases. *Ann. Surg.*, 129: 289 (Mar.) 1949.

The major causes of massive hematemesis in 300 consecutive cases were duodenal ulcer (57%), acute gastritis (14%), gastric ulcer (11%), and ruptured esophageal varix (8%). Four out of five patients were men. The over-all mortality was 25 per cent. Of the 75 patients who died, 71 did not receive a fraction of the blood which would have been required to replace the amount lost. When microscopic sections of the bleeding site

were examined postmortem, a partial or complete block of the eroded vessel by antemortem thrombus usually was found. This observation suggests that therapy should not be directed immediately toward surgical closure of the injured vessel but toward support of the depleted blood volume. Procedures which increased mortality were surgery, indwelling stomach tube with constant suction, gastric lavage, and active gastric diagnostic studies.

The author prefers the copper sulfate, falling drop method for following blood volume changes because of its simplicity and speed. In 73 patients with about the same age distribution as that of the 75 patients who died, adequate blood replacement and supportive treatment resulted in a mortality of but 4 per cent. Oral administration of a predigested protein-carbohydrate-vitamin mixture, and continuous sedation are recommended. There was no death from chronic peptic ulcer, the commonest cause of massive hematemesis, in the series of 73 patients.

LEMUEL C. MCGEE

KAY, A. W., JAMIESON, R. A., AND SMITH W. E. Hog-stomach extract and casein hydrolysate in peptic ulcer. *Brit. Med. J.*, 4603: 519 (Mar.) 1949.

The addition of a commercial extract of fresh hogs' stomachs to the diet of patients with peptic ulcer led to no symptomatic improvement. The preparation was considered to be nutritious but there was no evidence that it contained an anti-ulcer factor. The addition, to the customary diet, of an enzymic hydrolysate of fat-free whole milk, containing approximately equal parts of amino acids and readily assimilable carbohydrate, led to symptomatic improvement in only 2 of 12 patients, despite a gain in weight in all cases.

JOSEPH B. KIRSNER

FRASER, R. W. AND WEST, J. P. The management of bleeding duodenal ulcers. *Ann. Surg.*, 129: 299 (Mar.) 1949.

In 177 consecutive patients with moderate to severe hemorrhage from duodenal ulcer, the mortality was 6.2 per cent. Nonoperative treatment in 165 patients resulted in 7

deaths, a mortality rate of 4.2 per cent. On the other hand, 4 of 12 patients subjected to operation died. The authors feel that with but few exceptions, surgical treatment of bleeding duodenal ulcer should be limited to patients over 50 years of age. More generous use of blood transfusions has improved the nonoperative treatment of massive hemorrhage from peptic ulcer.

LEMUEL C. MCGEE

MCGINTY, D. A., WILSON, M. L., AND RODNEY, G. The ulcer-inhibiting action of pyrogens. *Proc. Soc. Exp. Biol. Med.*, 70: 334 (Feb.) 1949.

Urinary extracts, under investigation for ulcer-inhibiting action in the Shay rat, were found to contain a high concentration of pyrogens. Since other investigators had shown that pyrogens suppressed gastric motility in dogs, the effect of purified pyrogens was studied in the pylorus-ligated rat. Pyrogens were prepared from cultures of *B. prodigiosus*, *pseudomonas aeruginosa* and *E. typhi*. These pyrogens were found to be highly active ulcer-inhibiting substances. Whether the presence of such substances in tissue and urinary extracts may account for anti-ulcer activity remains to be investigated. The mode of action may be associated with diminished acidity and volume of gastric secretion. No evidence, however, of any general "toxicity" was seen in the animals which received purified pyrogens.

H. NECHELES

SURGERY

DEVINE, J. Suction applied to appendectomy. *Lancet*, 256: 223 (Feb.) 1949.

The author describes a method of removing the appendix under suction. The appendix is aspirated into a tube while it is being excised. This will prevent contamination of the field of operation and lessen wound infection.

PHILIP LEVITSKY

ROSEMOND, G. P., BURNETT, W. E., AND COOKE, F. N. One stage end-to-end anastomosis of the colon—An analysis of the complications in 79 cases with a comparison of open and aseptic types of anas-

tomoses. *Surg. Gyn. Obs.*, 88: 209 (Feb.) 1949.

The authors present a survey of 79 cases with end-to-end one-stage anastomosis of the colon, performed in the Temple University Hospital from 1945 to 1947. Postoperative complications were many and varied. There were 6 deaths; two were due to resulting coronary occlusion, and one to each of the following: Coronary occlusion and cerebral embolus from mural thrombus, peritonitis, small bowel obstruction, and sepsis.

The establishment of a proximal vent or safety valve at the time of operation is a controversial issue, but the authors conclude that, in low lesions, a tube through the anastomosis seems to eliminate the necessity of a proximal vent, whereas in uncomplicated resections, a proximal vent is unnecessary. In cases in which there is danger of obstruction or leakage, a proximal vent may be useful and can be used at the discretion of the surgeon.

FRANCIS D. MURPHY

PHYSIOLOGY: SECRETION

KAULSBERSZ, J., PATTERSON, T. L., SANDWEISS, D. J., AND SALTZSTEIN, H. C. The effect of urine extract from thyroidectomized dogs on gastric secretion. *Rev. Gastroenterol.*, 16: 257 (Mar.) 1949.

It has been shown that dogs deprived of ovaries do not excrete urogastrone in the urine in the quantities found in normal dogs. If thyroidectomy is combined with oöphorectomy, the inhibitory substance appears in the extracts in approximately normal quantities. When thyroidectomy was performed alone, the urine extract produced a pronounced inhibition of gastric secretion after histamine administration. The general character of the response indicated that the inhibitory principle of these extracts in every respect is similar to the "urogastrones" of the normal urine.

C. WILMER WIRTS, JR.

KAULSBERSZ, J., PATTERSON, T. L., SANDWEISS, D. J., AND SALTZSTEIN, H. C. The effect of urine extract from oöphorectomized dogs on gastric secretion. *Rev. Gastroenterol.*, 16: 254 (Mar.) 1949.

The effect of urine extracts on the gastric secretion of normal gastric fistula and Heidenhain pouch dogs following double histamine injections was studied. Total output of HCl for 70 minutes following histamine injection was regarded as a measure of gastric secretory response.

It was found that urine extracts from oöphorectomized dogs do not influence gastric secretion in response to histamine as normal urine extracts do. A similar finding was previously noted in the hypophysectomized dogs. These results would seem to indicate that little or no urogastrone is present in the urine of these types of dogs.

C. WILMER WIRTS, JR.

FRIEDMAN, M. H. F. AND SNAPE, W. J. Influence of secretin and insulin on pancreatic secretion in healthy human subjects. *Proc. Soc. Exp. Biol. Med.*, 70: 280 (Feb.) 1949.

Central vagus stimulation by insulin hypoglycemia is without effect on secretion of fluid by the pancreas in man and the unanesthetized dog. However, studies on the influence of insulin hypoglycemia on the secretion of enzymes have given inconsistent results.

In this study, 22 men and women with no evidence of gastrointestinal or metabolic disease were used. About 15 to 18 hours after the previous meal, stomach and intestine were intubated with a double-lumen tube, as described by Agren and Lagerlof. Location of the tube was verified by fluoroscopy. Separate gastric and duodenal samples were collected. Secretin, Wyeth was administered intravenously 1.1 clinical units per kg. body weight. Continuous collection of separate gastric and intestinal contents was done for the next 60 minutes. A second dose of secretin was then given and collection continued for the next hour. In one series, the second intravenous dose of secretin was combined with crystalline insulin (0.1 unit per kg. body weight). In some experiments a third injection of either secretin alone, or of secretin combined with insulin, was made at the end of the second hour and collection continued during the third hour.

It was found that during insulin hypogly-

cemia the concentration and output of pancreatic enzymes was increased but that the volume of secretion was not influenced.

H. NECHELES

METABOLISM AND NUTRITION

BERGEIM, O. AND KIRCH, E. R. Reduction of iron in the human stomach. *J. Biol. Chem.*, 177: 591 (Feb.) 1949.

Experiments were conducted on 10 normal medical students to determine whether, by using a number of common foods, reduction of iron would occur in the human stomach, comparable to that observed in artificial gastric digestion. This work emphasizes the possibility that gastric reduction may be a primary factor in facilitating iron absorption by the body.

Iron, present in foods or added to a variety of foods particularly those containing ascorbic acid, was found to be reduced in the human stomach to a significant degree. Such foods as breads, meats, and fruits, gave iron reductions as high as 50-90 per cent. The results with milk and eggs were somewhat irregular. Ascorbic acid, as well as proteins and protein digestion products, was considered a factor in iron reduction, as was the formation of complexes of iron with certain food constituents. Further studies and observations on certain foods must be made, as it is not yet clear what other reducing substances may be involved.

FRANCIS D. MURPHY

ARIEL, I. M. The nature of post-operative hypoproteinemia in patients with gastrointestinal cancer. *Surg. Gyn. Obs.*, 88: 185 (Feb.) 1949.

One hundred patients with gastrointestinal cancer have been studied by the author, with special reference to the incidence and degree of hypoproteinemia. The cause of the hypoproteinemia is not entirely clear, although deficient diets, repeated hemorrhage, defect in the absorption of amino acids, increased catabolism of the protein and other metabolic abnormalities, which prevent the synthesis of serum proteins, have been considered.

The effect of surgery upon plasma protein concentrations was also studied. Patients

were divided into three groups: (1) Those with gastrointestinal cancer, (2) those with benign non-neoplastic diseases of the gastrointestinal tract, and (3) those women with gynecological disorders. The findings indicate that concentrations of serum protein in patients with gastrointestinal cancer are low before operation and fall still lower after operation, which would seem to indicate the reason for the high incidence of wound disruption, electrolyte disturbances, adynamic ileus and gastrointestinal and peripheral edema. Following cancer resection and after careful preoperative and postoperative care, serum protein levels returned to normal.

This study also indicates that there is no correlation between liver protein concentration of serum protein, and while there are certain alterations in liver proteins, the liver cannot supply plasma protein during surgical stress.

FRANCIS D. MURPHY

MISCELLANEOUS

BLEGEN, H. M. Surgery in situs inversus. *Ann. Surg.*, 129: 244 (Feb.) 1949.

It is of interest that Aristotle first described the anomaly of situs inversus in animals; in the 17th century, it was recognized in man. Statistical consideration shows that situs inversus will be encountered once in every 6,000-8,000 individuals.

The author has collected information from the records of 158 surgical operations performed on 144 patients with situs inversus. In this series, an error in diagnosis before operation occurred in 45 per cent of the cases. The transposition was recognized during surgery in 32 per cent. In 13 per cent, the bewilderment of the surgeon was such that the condition was not recognized even at the time of operation. Subsequent X-ray studies yielded the diagnosis in this group. As a result, an incorrect surgical incision was made in 31 per cent of the patients and, in 12 per cent, the abdomen was closed without accomplishing the operative aim. In one-third of the instances of left-sided appendicitis, there was reported false projection of the pain; i.e., localized pain in the right side of the abdomen.

LEAUEL C. MCGEE

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STUDIES ON ADRENAL CORTICAL FUNCTION IN CANCER

I. ACUTE EFFECTS OF ADRENOCORTICOTROPHIC HORMONE IN PATIENTS WITH GASTRIC CANCER*

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From the Section on Clinical Endocrinology, Division of Clinical Investigation, The Sloan-Kettering Institute, Memorial Hospital Cancer Center, New York

Previous studies from this institute by Dr. Konrad Dobriner and his associates have suggested that patients with cancer have disordered function of the adrenal cortex¹. The evidence includes: 1) the finding that an abnormal steroid metabolite of adrenal cortical origin, 11-hydroxy-etiocholanolone, is excreted in the urine by patients with various types of cancer; 2) the demonstration that this same abnormal steroid is excreted also by patients with adrenal cortical hyperfunction of the Cushing's syndrome type; 3) the observation that in patients with cancer there is, after a damaging event, a decreased response in the urinary excretion of steroids with adrenal cortical activity; and 4) the finding that adrenal cortical extract must be given with glucose feeding to induce normal liver glycogen deposition in patients with gastric cancer. We have reported recently before the American Association for Cancer Research² that the abnormal steroid metabolite, 11-hydroxy-etiocholanolone, was excreted by two men and two women with advanced gastric cancer.

Because of this evidence we have compared the adrenal cortical function of a series of patients with gastric cancer† with that of a suitable group of control cases not suffering from malignant or adrenal cortical disease‡. As a test procedure we have determined the immediate response of the adrenal cortex to the administration of an anterior pituitary adrenocorticotrophic hormone preparation, hereafter called ACTH§. The response to this hormone preparation

* These investigations were supported (in part) by a grant from the National Cancer Institute, United States Public Health Service. Read at the Annual Meeting of the American Gastroenterological Association, Atlantic City, June 9, 1949.

† We are indebted to Dr. George T. Pack, Dr. Gordon P. McNeer and their associates of the Gastric and Mixed Tumor Service of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, of the Memorial Hospital Cancer Center, New York, for their cooperation in making these patients available to us.

‡ We acknowledge our indebtedness to Dr. George W. Thorn and his associates of the Peter Bent Brigham Hospital, Boston, for permitting us to incorporate in the control series the data on some of the cases studied in Boston.

§ We are grateful to Dr. John R. Mote, of the Armour Laboratories, Chicago, for generous supplies of anterior pituitary adrenocorticotrophic hormone (ACTH).

has been measured in terms of the alterations in the blood eosinophile level and in the urinary excretion of creatinine, uric acid, phosphorus, and potassium.

The test procedure employed, hereafter called "The Four-Hour ACTH Test", was devised by Dr. George Thorn and his associates, for determining adrenal cortical function in patients suspected of having Addison's disease. They have shown³ that the intramuscular administration of 25 mg. of ACTH will

FOUR HOUR ACTH TEST (25mg.)

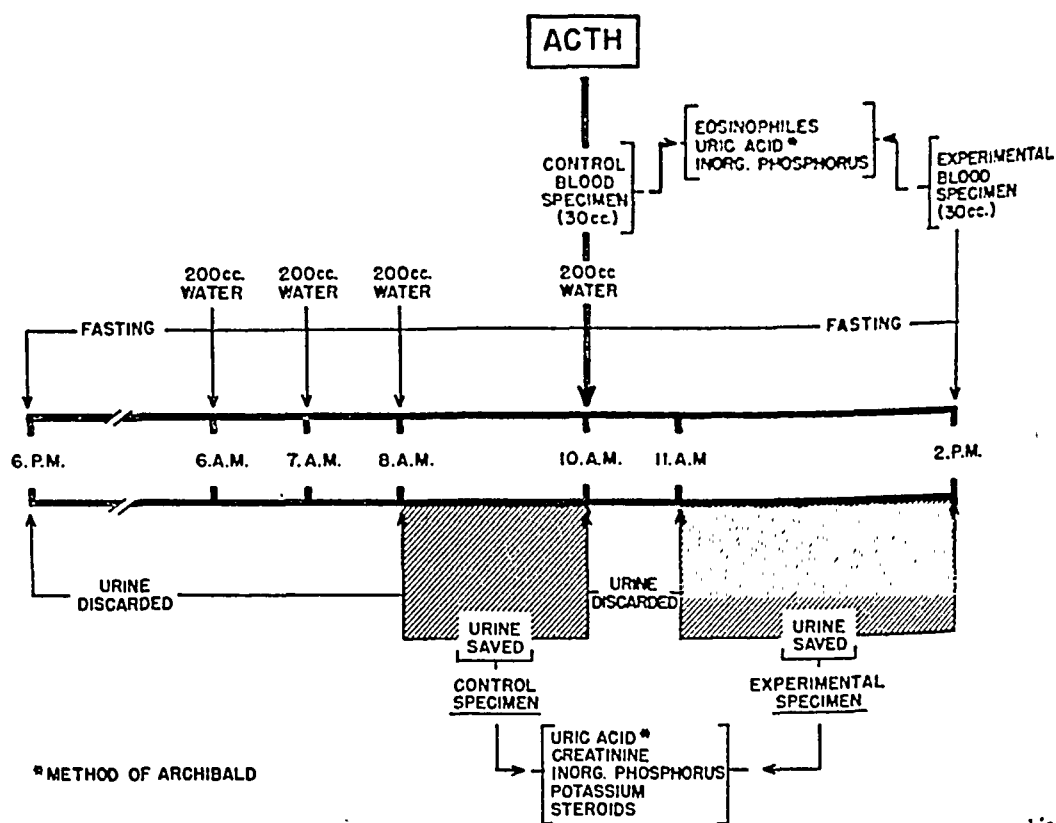


FIG. 1. Graphic Representation of Procedure Employed in the Four-Hour Adrenocorticotrophic Hormone (ACTH) Test.
For discussion, see text.

cause within four hours a fall in the number of circulating eosinophiles in the blood and a rise in the urinary uric acid/creatinine ratio in individuals who have normal adrenal cortical function. The Thorn procedure has been followed exactly by us except that some additional end-points have been measured. In the material presented here the dose of ACTH was always equivalent to 25 mg. of the Armour standard.

The test procedure is outlined in Fig. 1. The subject begins to fast at 6 p.m. on the day before the test, and continues until it is completed the next day

at 2 p.m. Water (200 cc.) is given at 6, 7, 8, and 10 a.m. to provide fluid for urine flow. The urine is discarded from 6 p.m. to 8 a.m., and from 10 to 11 a.m. The control specimen of urine (2 hours) is collected from 8 to 10 a.m. and the experimental specimen (3 hours) from 11 a.m. to 2 p.m. The control

CHANGES IN CIRCULATING EOSINOPHILES

FOUR HOUR ACTH TEST (25 mg.)

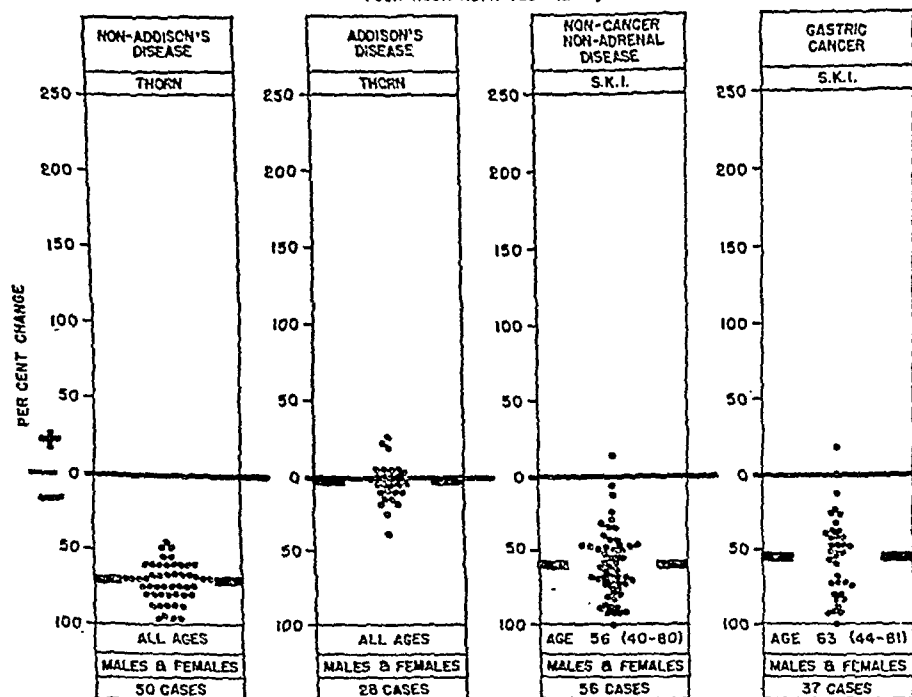


FIG. 2. Changes in Circulating Eosinophiles during Four-Hour ACTH Test in Patients of All Ages and Both Sexes with Non-Addison's Disease; with Addison's Disease; with Non-Cancer, Non-Adrenal Disease; and with Gastric Cancer.

The average values are indicated by the heavy bars. The average age and the range of ages of the patients are given. Thorn = data obtained from Dr. George W. Thorn; S.K.I. = data obtained at Sloan-Kettering Institute. For discussion, see text.

specimen of blood (30 cc.) is withdrawn at 10 a.m., and following this the ACTH is given intramuscularly. The experimental specimen of blood (30 cc.) is withdrawn at 2 p.m. The determinations performed on these specimens are shown in the figure.

The data on the changes in circulating eosinophiles for males and females of all ages in terms of per cent change from the initial value are shown in Fig. 2. In the first column, the 50 cases of non-Addison's disease reported by Dr. Thorn showed a consistent fall that averaged 70 per cent; in contrast in the

second column, the 28 cases of Addison's disease reported by Dr. Thorn exhibited practically no change with an average figure of minus five per cent. Our data are given in columns 3 and 4. It will be seen that the 56 cases of non-cancer, non-adrenal disease responded with a consistent fall which averaged 60 per cent, while the 37 cases of gastric cancer also showed a consistent fall which averaged 55 per cent. Thus, by this index, no evidence of adrenal cortical un-

CHANGES IN URINARY URIC ACID/CREATININE RATIO

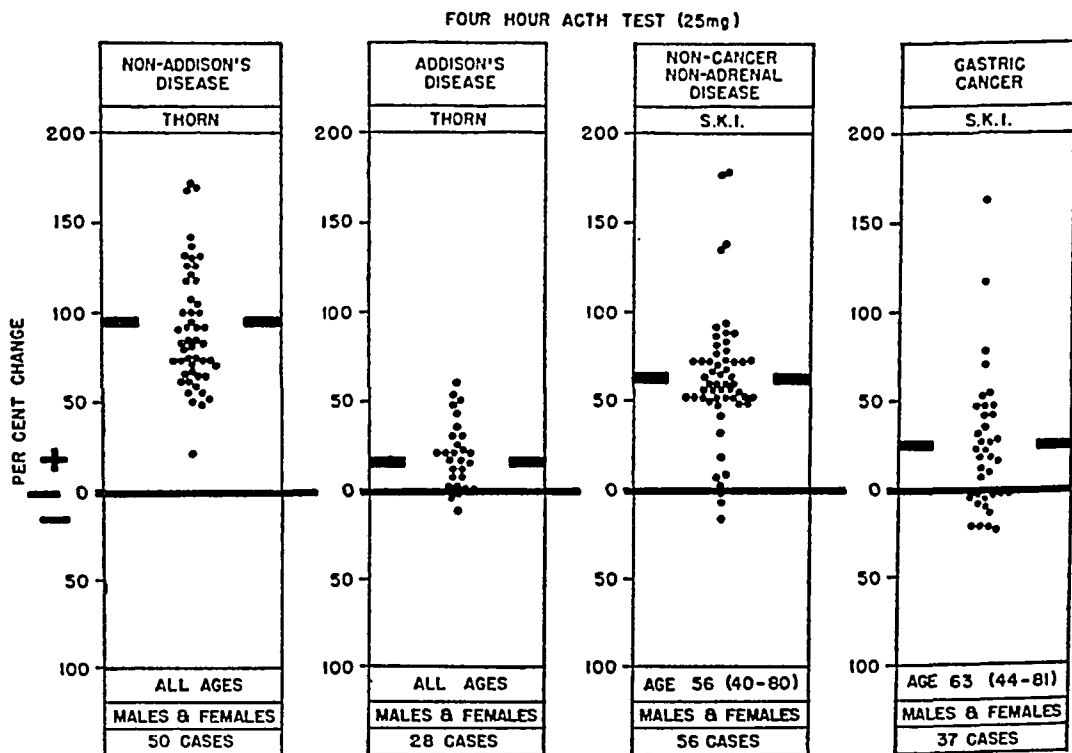


FIG. 3. Changes in Urinary Uric Acid/Creatinine Ratio during Four-Hour ACTH Test in Patients of All Ages and Both Sexes with Non-Addison's Disease; with Addison's Disease; with Non-Cancer, Non-Adrenal Disease; and with Gastric Cancer.

The average values are indicated by the heavy bars. The average age and the range of ages of the patients are given. Thorn = data obtained from Dr. George W. Thorn; S.K.I. = data obtained at Sloan-Kettering Institute. For discussion, see text.

responsiveness is demonstrated in gastric cancer such as is found in Addison's disease.

In Fig. 3 are given the data on the changes in urinary uric acid/creatinine ratio for the corresponding groups of cases. There was a significant rise in the 50 cases of non-Addison's disease (column 1) which averaged 90 per cent, and in our 56 cases of non-cancer, non-adrenal disease (column 3) which averaged 63 per cent. In contrast, the 28 cases of Addison's disease (column 2) and the 37 cases of gastric cancer (column 4) showed insignificant rises which averaged

15 and 24 per cent respectively. Thus, to this index, the adrenal cortex was unresponsive in gastric cancer as it was in Addison's disease.

It will be noted in Fig. 3 that some of our non-cancer, non-adrenal disease cases failed to respond, in contrast to the cases of non-Addison's disease of Dr. Thorn. We are informed by him that his group contained no patients with

FOUR HOUR ACTH TEST (25mg)
AVERAGE CHANGES IN MALES
(54 YEARS AND OVER)

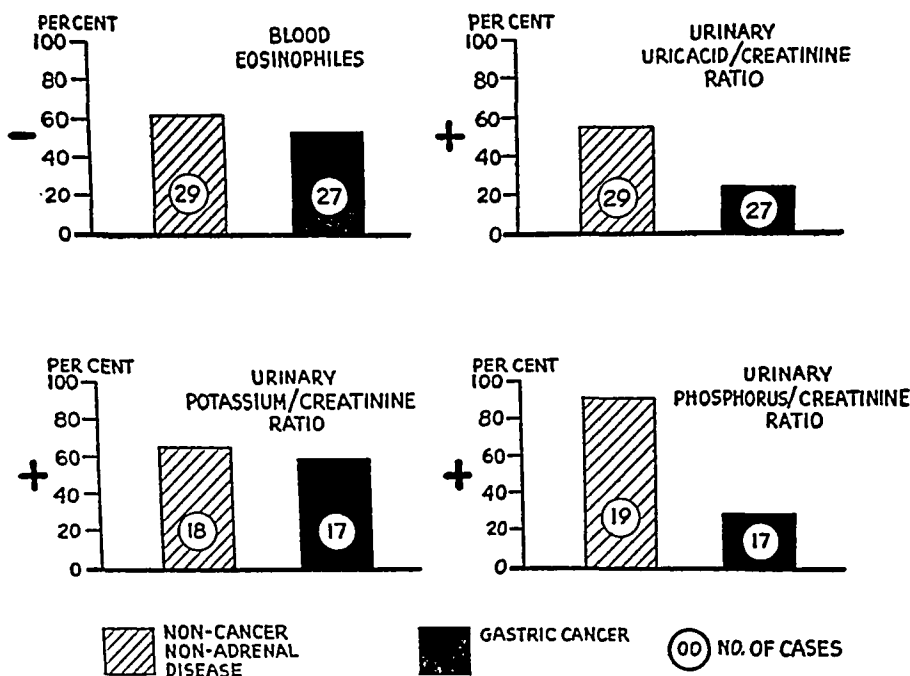


FIG. 4. Average Changes in Males 54 Years of Age and Over in the Circulating Eosinophiles, the Urinary Uric Acid/Creatinine Ratio, the Urinary Potassium/Creatinine Ratio, and the Urinary Phosphorus/Creatinine Ratio during the Four-Hour ACTH Test by Patients with Non-Cancer, Non-Adrenal Disease and by Patients with Gastric Cancer.

The hatched bars are the averages for the non-cancer, non-adrenal cases, and the solid bars are the averages for the gastric cancer patients. The figures in the circles are the number of cases in the groups. For discussion, see text.

cancer, and were for the most part younger than our cases. Examination revealed that all of our cases in the non-cancer, non-adrenal group who failed to respond were elderly men. Furthermore, gastric cancer occurs predominantly in older males. Our data were analyzed, therefore, in terms of age and sex. It was found that whereas there was a tendency for the adrenal cortex of men of 54 years of age and over to become unresponsive in terms of the uric acid/creatinine ratio response to ACTH, the same significant difference in response

was found between the non-cancer, non-adrenal disease cases and the patients with gastric cancer when they were compared on this age and sex basis. The details of these comparisons will be reported elsewhere.

We have also determined the urinary inorganic phosphorus/creatinine ratios and the urinary potassium/creatinine ratios in our cases. The details cannot be given here, but the average values for male patients 54 years of age and over are compared for the two disease groups in Fig. 4. In these older males the following averages were obtained in the non-cancer, non-adrenal group and the gastric cancer group respectively: for changes in blood eosinophiles minus 61 per cent (29 cases) and minus 54 per cent (27 cases); for changes in urinary uric acid/creatinine ratio plus 54 per cent (29 cases) and plus 20 per cent (27 cases); for changes in urinary phosphorus/creatinine ratio plus 92 per cent (19 cases) and plus 28 per cent (17 cases); and for changes in urinary potassium/creatinine ratio plus 66 per cent (18 cases) and plus 58 per cent (17 cases).

The patients whose data are given in Fig. 4 were found on study to be comparable not only in sex and age, but in state of nutrition, occurrence of anemia, and condition of renal function. The serum uric acid, inorganic phosphorus, and potassium levels were determined before and after the administration of ACTH in 81, 69, and 20 cases respectively without uncovering any consistently significant deviations. The initial values for the uric acid/creatinine ratios and for the phosphorus/creatinine ratios ranged between 0.2 and 1.0 in the patients with gastric cancer, and differed in no significant way from the initial values for these ratios in the patients with non-cancer, non-adrenal disease. Insufficient data are available at present to warrant a discussion of the excretion of steroid metabolites during this test, of the effect of changes in the dosage of ACTH on it, or of the response of patients with other types of malignant disease to it.

DISCUSSION

The data show that the adrenal cortex of most patients with gastric cancer does not respond to stimulation with 25 mg. of anterior pituitary adrenocorticotrophic hormone in the same manner as does that of patients with diseases that do not involve malignancy or the adrenal cortex. This is evidence that there is a dysfunction of the adrenal cortex in these patients with gastric cancer.

The dysfunction demonstrated with this dose of ACTH is not, however, a complete adrenal cortical unresponsiveness, because failure to respond occurred with only two of the four indices (the uric acid/creatinine ratio, and the phosphorus/creatinine ratio), and ability to respond apparently normally was present by the other two indices (the eosinophile level, and the potassium/creatinine ratio). It remains to be determined in patients with gastric cancer

whether the "25 mg.-unresponsive indices" can be made to respond with larger doses of ACTH, or whether the "25 mg.-responsive indices" will fail to respond to smaller doses that are sufficient to bring out normal changes in patients with other types of disease. On the other hand, the "25 mg.-unresponsive indices" may be more sensitive measures of adrenal cortical function, and thus may be lost in the dysfunction of the adrenal cortex in the patients with gastric cancer, before the "25 mg.-responsive indices".

The dysfunction of the adrenal cortex found in patients with gastric cancer is demonstrated to differ from that found in Addison's disease, since in the former, the circulating eosinophiles respond, while in the latter they do not. Whether this difference is qualitative or quantitative remains to be determined. The lack of response to ACTH by the two indices in the patients with gastric cancer may be an indication that in these patients the adrenal cortex in certain respects is either not functioning, or is functioning to the limit of capacity, and, therefore, cannot be stimulated to further activity of the sort that leads to alterations measured by these two indices.

There is no evidence at present to establish whether the adrenal cortical dysfunction arises because of the cancer, whether the cancer arises because of the adrenal cortical dysfunction, or whether they both arise because of some third factor.

SUMMARY

Additional evidence is presented that patients with gastric cancer have adrenal cortical dysfunction. This evidence includes a failure to obtain the increases in the urinary uric acid/creatinine ratio and in the urinary inorganic phosphorus/creatinine ratio which are shown by patients with non-neoplastic, non-adrenal diseases, when the adrenal cortex is stimulated by 25 mg. of anterior pituitary adrenocorticotrophic hormone. The difference in the response of these two groups of patients is significant in spite of the tendency for the adrenal cortex to become less responsive in older male individuals. Some of the characteristics of the adrenal cortical defect in the patients with gastric cancer are discussed.

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THE UPTAKE OF RADIOACTIVE PHOSPHORUS BY GASTRIC CARCINOMA IN THE HUMAN*†

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From the Medical Clinic of the Peter Bent Brigham Hospital, and the Department of Medicine and the Biophysical Laboratory, Harvard Medical School, Boston, Massachusetts

Tumors which have been produced experimentally in animals are known to take up and incorporate radioactive phosphorus at a more rapid rate than the normal tissues. This has been demonstrated in experimental leukemia, hepatoma and other tumors.¹⁻⁴

The uptake of radioactive phosphorus by naturally occurring human cancers, however, has not been investigated until very recently, and there have been no studies of the uptake of radioactive phosphorus by gastric cancer, one of the most common of human malignancies.

We have been interested in gastric cancer, particularly, because it remains an enigma in early diagnosis and treatment as evidenced by an estimated death rate of 40,000 per year.

The purpose of this study is to measure the uptake and turnover rate of radioactive phosphorus in gastric cancer and in the non-cancerous gastric mucosa, and to compare their phosphorus contents. In order to obtain further information upon the distribution of phosphorus within the tissue components, chemical fractionation of the normal mucosa and the tumor into the acid soluble, lipid and protein phosphorus fractions was performed, and the radioactivity of each was measured.

In view of the fact that the antrum and lesser curvature of the stomach are the site of approximately 70 per cent of gastric cancers, these areas were compared individually with the duodenal mucosa adjacent to the pylorus where carcinoma is unknown.

The greater curvature (where 60% of ulcers are malignant) was compared to the antrum and lesser curvature where only 17% of ulcerating lesions are found to be malignant.

Finally, the uptake of radioactive phosphorus by the atrophic gastric mucosa, which many consider to be a precancerous mucosa, was compared to the uptake of the essentially normal gastric mucosa of patients with duodenal ulcer.

* This work was supported in part by the Office of Naval Research.

† Read at the Annual Meeting of the American Gastroenterological Association, Atlantic City, June 9, 1949.

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§ Present Address: Radiation Laboratory, University of California, Berkeley 4, California.

METHODS

These studies were made on patients undergoing subtotal gastric resection either for gastric cancer or for duodenal or gastric ulcer. All patients were gastroscoped prior to surgery, and the macroscopic appearance of the normal

TABLE I
Clinical data on patients injected with radioactive phosphorus

NAME	WEIGHT	AGE	SEX	TIME BE- TWEEN OPERA- TION AND IN- JECTION	DIAGNOSIS	REMARKS
	kg.			hrs.		
C. M.	44.4	54	M	40	Chronic cicatrizing duodenal ulcer	Gastric mucosa essentially normal by gastroscopic and histological examination Gastric mucosa normal elsewhere
J. M.	59.0	33	M	42	Active duodenal ulcer	
J. C.	61.4	68	M	44	Benign gastric ulcer on lesser curvature	
M. M.	48	43	F	40	Chronic duodenal ulcer with obstruction	
M. E.	54.4	68	M	45	Polypoid adenocarcinoma of the cardia	Severe atrophic gastritis
S. A.	60.4	60	M	38	Ulcerating carcinoma of gastric antrum	Atrophic gastritis
S. K.	73.2	57	M	41	Ulcerating carcinoma of lesser curvature—lower third—anterior wall of stomach	Atrophic gastritis
M. W.	43.8	66	F	29	Ulcerating carcinoma of greater curvature—posterior wall—middle third of stomach	Atrophic gastritis
K. O.	66	60	F	42	Ulcerating carcinoma of gastric fundus with extensive metastases	Atrophic gastritis
E. F.	34.4	78	F	24	Linitis plastica	Diffuse involvement of entire stomach

mucosa and the tumors were confirmed by the histological examination of the resected specimens. The diagnosis of atrophic gastritis was confirmed by microscopic examination. The pertinent clinical data of the four ulcer patients and the six patients with gastric cancer are recorded in Table I.

Radioactive phosphorus as $\text{KH}_2\text{P}^*\text{O}_4$ was furnished by the Clinton Laboratory at Oak Ridge, Tennessee, and solutions were prepared and standardized by R. F. Cowing of the New England Deaconess Hospital. The original sample

was suitably diluted with distilled water and autoclaved. This neutral solution was administered intravenously approximately 36 hours prior to the scheduled time of operation. The chosen dose of 1 microcurie per pound of body weight was based on calculations by Cowing⁶ which showed that this would lead to a total body irradiation of not more than 1.5 r.

Within one hour after removal of the stomach the mucosa was stripped from the stomach wall and prepared for analysis. In the non-cancerous stomachs mucosa was taken from the greater curvature, lesser curvature, and pre-pyloric area; duodenal samples were obtained whenever possible. In the tumor-bearing stomach the position of the lesion was usually such that normal samples of all the areas could not be obtained. Consequently, a sample of normal appearing mucosa as far from the lesion as possible was taken. Histological study later showed that there were no malignant cells in the areas taken as non-cancerous. In the ulcerating tumors the samples were taken from the actively growing edge of the lesion.

The following analyses were performed:

Total Phosphorus: 300 mg. of tissue were dried in an oven at 110° C for two to three hours and then digested with 10 N H₂SO₄ and superoxol.

Acid Soluble Phosphorus: (inorganic phosphate, ester phosphate, adenylic acid, adenosine diphosphate, adenosine triphosphate, creatine phosphate, etc.) 400 mg. of tissue were minced with scissors and ground with 10% trichloroacetic acid in a small glass Potter-Elvehjem tissue homogenizer. The filtrate was digested with 10 N H₂SO₄ and superoxol.

Lipid Phosphorus: (lecithins, cephalins, sphingomyelins, etc.) 500 mg. of tissue were finely minced with scissors and ground in the homogenizer with 1:1 ethyl alcohol-ether mixture. The homogenate was then extracted with two successive portions of alcohol-ether mixture on the steambath for periods of 30 minutes each. The combined extracts were evaporated to dryness and digested with 10 N H₂SO₄ and superoxol.

Protein Phosphorus: (chiefly nucleoprotein, but includes some phosphoprotein which does not yield nucleic acid upon hydrolysis). This fraction was calculated as the difference between the total phosphorus and the sum of the acid soluble and the lipid fractions.

After the digestion, each sample was diluted to a suitable volume and aliquots were taken of the same sample for counting in solution with a Geiger-Mueller dipping counter⁶ and for determination of the phosphorus content by the method of Fiske and SubbaRow⁷. The errors of the chemical determination were about 5%, while the counting errors were as high as 10%. The protein phosphorus values, being calculated as differences, have larger errors than the other determinations. Values given in the tables represent averages of duplicate determinations.

TABLE II
Phosphorus content of various areas of non-cancerous stomachs

NAME	TOTAL PHOSPHORUS				ACID SOLUBLE PHOSPHORUS				LIPID PHOSPHORUS				PROTEIN PHOSPHORUS			
	Greater Curva- ture	Lesser Curva- ture	Pylorus	Duo- denum	Greater Curva- ture	Lesser Curva- ture	Pylorus	Duo- denum	Greater Curva- ture	Lesser Curva- ture	Pylorus	Duo- denum	Greater Curva- ture	Lesser Curva- ture	Pylorus	Duo- denum
	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm
C. M.	0.0668	0.0680	0.0577		0.0205	0.0205	0.0212		0.0221	0.0173	0.0123		0.0242	0.0302	0.0242	
J. M.	0.0706	0.0461	0.0513	0.0674	0.0205	0.0152	0.0168	0.0158	0.0213	0.0102	0.0121	0.0205	0.0288	0.0207	0.0224	0.0311
J. C.	0.0697	0.0436			0.0237	0.0150			0.0155	0.0117			0.0305	0.0169		
M. M.			0.0568	0.0680			0.0162	0.0164			0.0125	0.0203			0.0280	0.0313
Average.....		0.0605					0.0183				0.0159				0.0262	
S. D.....		.00984					.00295				.00466				.00510	

Expression of Results: Results have been expressed as *Biological Concentration Coefficient*³

$$\text{BCC} = \frac{\text{counts per min. found in sample/mM}}{\text{counts per min. injected/gm body weight}} \times 100$$

The counts per minute found in the sample per millimole of phosphorus were expressed as fractions of the injected dose. The injected dose was cal-

TABLE III
Phosphorus content of gastric cancer and of non-cancerous gastric mucosa

NAME	DIAGNOSIS	TOTAL PHOSPHORUS MM/GM TISSUE		ACID SOLUBLE PHOSPHORUS MM/GM TISSUE		LIPID PHOS- PHORUS MM/GM TISSUE		PROTEIN PHOSPHORUS MM/GM TISSUE	
		Cancer	Non- Cancer	Cancer	Non- Cancer	Cancer	Non- Cancer	Cancer	Non- Cancer
C. M.	Non-cancer		0.0642		0.0207		0.0172		0.026
J. M.	Non-cancer		0.0590		0.0170		0.0160		0.026
J. C.	Non-cancer		0.0568		0.0194		0.0136		0.024
M. M.	Non-cancer		0.0602		0.0158		0.0163		0.028
Mean.....	Non-cancer		0.0600		0.0182		0.0157		0.026
M. E.	Cancer	0.0823	0.0329	0.0202	0.0120	0.0177	0.0100	0.045	0.011
S. A.	Cancer	0.0771	0.0579	0.0234	0.0222	0.0171	0.0146	0.038	0.020
S. K.	Cancer	0.0374	0.0635	0.0224	0.0229	0.0100	0.0162	0.005	0.025
M. W.	Cancer	0.0510	0.0435	0.0159	0.0172	0.0148	0.0121	0.020	0.014
K. O.	Cancer	0.0558		0.0161		0.0114		0.028	
E. F.	Cancer	0.0539		0.0211		0.0136		0.019	
Mean.....	Cancer	0.0597	0.0494	0.020	0.019	0.0140	0.0132	0.025	0.017
Overall mean*.....		0.0597	0.0547	0.020	0.019	0.014	0.014	0.025	0.021
Diff. between means.....		+0.005 = 9%		+0.001 = 2%		± 0 = 0%		+0.0045 = 2%	
Probability.....		p = 0.5		p = 0.5		p = 1		p = 0.5	

* Mean of all non-cancerous mucosa, regardless of whether stomach bears a cancer.

culated by counting a standard solution of the radioactive phosphorus on the same day as the tissue samples were counted. The coefficient is expressed in terms of body weight in order to compare different patients on the basis of equivalent doses. The factor of 100 is arbitrary.

The biological concentration coefficient is proportional to the phosphorus turnover. The value is a coefficient which has no dimensions and is not additive.

All data have been analyzed statistically. Fisher's "t" test was used throughout as a criterion of significance⁹.

TABLE IV
The uptake of radioactive phosphorus by different areas of the non cancerous stomach
(Expressed as Biological Concentration Coefficients)

NAME	TOTAL PHOSPHORUS				ACID SOLUBLE PHOSPHORUS				LIPID PHOSPHORUS				PROTEIN PHOSPHORUS			
	Greater Curva- ture	Lesser Curva- ture	Pylorus	Duo- denum	Greater Curva- ture	Lesser Curva- ture	Pylorus	Duo- denum	Greater Curva- ture	Lesser Curva- ture	Pylorus	Duo- denum	Greater Curva- ture	Lesser Curva- ture	Pylorus	Duo- denum
	mM/gm	mM/gm	mM/gm	mM/mg	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm	mM/gm
C. M.	2956	2821	3059		4216	3596	3998		2460	2501	2662		3007	1084	2511	
J. M.	2969	3782	3379	3379	5836	3673	6014	5666	3162	3596	3720	2791	1364	2418	3812	2697
J. C.	4929	5860			6541	9672			5612	7285			3379	1643		
M. M.			3140	3520			6020	5760			2850	2862			2910	2815
Average.....	3617.6				5726.5				3591				2512.7			

RESULTS

Phosphorus Content: The phosphorus content of different areas of the non-cancerous stomachs is essentially the same for each fraction (Table II). The chemical composition of the duodenal mucosa does not differ from that of the antrum in respect to phosphorus. Applying Fisher's "t" test to the data in the table, we find that they are statistically homogeneous. There is no

TABLE V

The uptake of radioactive phosphorus by gastric cancer and by non-cancerous gastric mucosa
(Expressed as Biological Concentration Coefficients)

NAME	DIAGNOSIS	TOTAL PHOSPHORUS BCC		ACID SOLUBLE PHOSPHORUS BCC		LIPID PHOSPHORUS BCC		PROTEIN PHOSPHORUS BCC	
		Cancer	Non-Cancer	Cancer	Non-Cancer	Cancer	Non-Cancer	Cancer	Non-Cancer
C. M.	Non-cancer		2945		3937		2541		2201
J. M.	Non-cancer		3379		5797		3317		2573
J. C.	Non-cancer		5394		8122		6448		2511
M. M.	Non-cancer		3330		5890		2850		2862
Mean.....	Non-cancer		3762		5936		3789		2536
M. E.	Cancer	4495	3689	5,921	5642	5239	3813	3503	1643
S. A.	Cancer	6851	4588	8,711	7099	5332	3782	6448	2511
S. K.	Cancer	5766	3875	7,161	8711	5425	5432	3224	0
M. W.	Cancer	5983	3999	10,323	8215	4743	3968	3379	0
K. O.	Cancer	7533		11,470		8432		4991	
E. F.	Cancer	4526		6,603		5456		2760	
Mean.....	Cancer	5859	4037	8,364	7416	5804	4248	4051	1038
Overall mean*.....		5859	3899	8,364	6676	5804	4018	4051	1787
Diff. between means.....		1960 = 48.5%		1688 = 25.2%		1786 = 44.4%		2264 = 126%	
Probability.....		p = 0.01		p = 0.05		p = 0.01		p = 0.02	

* Mean of all non-cancerous mucosa, regardless of whether stomach bears a cancer.

value that varies from the mean of the series by more than could be accounted for by chance. Therefore, the average of these results may be considered to be the mean phosphorus content of the non-cancer-bearing stomach, irrespective of the area of origin.

Table III shows the mean phosphorus content of all the stomachs studied. When non-cancerous stomachs are compared with the non-cancerous portions of cancer-bearing stomachs, there is again no demonstrable difference in the phosphorus content. Therefore, all the non-cancerous mucosae have been grouped as controls and compared with the cancer tissue. The difference in the

means of the cancer and the control group is insignificant. Thus, the phosphorus content is the same for all the tissues studied, whether normal or malignant. The same results are found when each of the phosphorus fractions is studied individually.

UPTAKE OF RADIOACTIVE PHOSPHORUS

When the uptake of radioactive phosphorus (expressed as a biological concentration coefficient) is studied, a difference between the cancer and non-cancerous mucosa can be demonstrated (Table V). The uptake of total phosphorus by tumor tissue is 48.5% greater than that of non-cancerous mucosa.

THE MEAN UPTAKE OF RADIOACTIVE PHOSPHORUS
BY GASTRIC CANCER AND BY NON-CANCEROUS GASTRIC MUCOSA

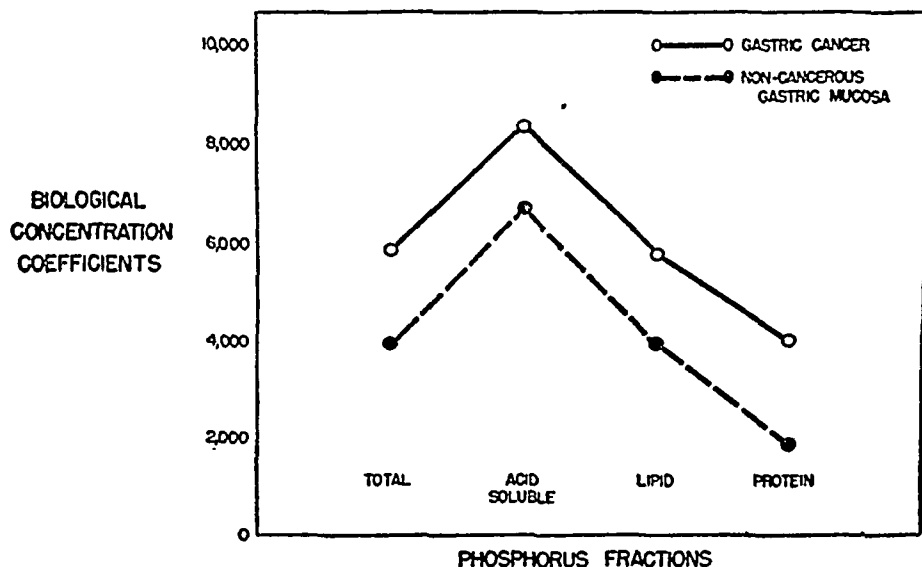


FIG. 1

There is no significant difference in the uptake or turnover rate of the acid soluble fraction, but the 44% increase in the lipid phosphorus and the 126% increase in the protein phosphorus fractions in the tumor tissue are significant (Table V).

The biological concentration coefficients of the various regions of the normal stomach are the same for each fraction, and the use of an average value is therefore justified (Table IV). There is no significant difference, furthermore, between the non-cancerous mucosa from the cancer-bearing stomach and the mucosa from a stomach that does not bear a cancer (Table V). Therefore, all the non-cancerous samples of mucosa are grouped together regardless of the presence or absence of cancer in other parts of the stomach and their average uptake (biological concentration coefficient) compared to that of the

cancer tissue. The increased uptake of radioactive phosphorus by gastric cancer in the total, acid soluble, lipid and protein phosphorus fractions is summarized in Figure 1.

DISCUSSION

Phosphorus Content: That the chemical composition of the various phosphorus fractions is the same in gastric cancer as it is in normal tissue is in contrast to the work of Kishi, Fujiwara, and Nakahara¹⁰ who reported a decreased lipid phosphorus in experimental hepatomas. A low lipid phosphorus content has been reported in human lung tumors by Lustig¹¹, and there appears to be a decrease in the lipid phosphorus in brain tumors as well. Whether a normal lipid phosphorus fraction is characteristic only of the gastric cancer cannot be stated at present.

Turnover: This investigation was undertaken not only to determine the rate at which radioactive phosphorus is taken up by the gastric cancer but to measure its rate of turnover, i.e., the replacement of the phosphorus already present by the newly added radioactive phosphorus. This may be expressed in terms of specific activity (counts per minute per millimole of phosphorus) or as a biological concentration coefficient which further takes into account the injected dose of radioactivity and the weight of the patient.

It has been shown that the constituents of a tissue are not static but are in dynamic equilibrium. There is a continuous building up and breaking down of tissue. When a tissue remains constant in size the number of atoms lost must equal the number being added. The ratio of the atoms added per unit of time to the total atoms of that element present in the tissue is known as the rate of turnover¹². Although this value cannot be determined absolutely except in special cases, relative rates of turnover can be estimated by comparing biological concentration coefficients.

As labeled atoms are incorporated into a tissue their concentration rises rapidly and linearly at first and then slowly levels off to a maximum value. During the linear portion of the uptake curve the amount of tracer in the tissue will be proportional to the number of new atoms being added, since the number of labeled atoms present is so small that their loss is negligible compared to the total number lost. Therefore, when radioactive phosphorus is administered to a patient and the biological concentration coefficient is determined soon thereafter, the biological concentration coefficient is proportional to the phosphorus turnover during the experimental period.

The rate of phosphorus turnover is at least 48.5% higher in gastric cancer than in non-cancerous gastric mucosa. This is in accord with the results found in tumors in experimental animals¹⁻³.

When the acid-soluble phosphorus compounds were studied the turnover

rates in cancer and non-cancerous mucosa were found to be essentially the same.

The lipid phosphorus turnover is at least 44% higher in the tumor than in the non-cancerous tissue. Cell phospholipids are present usually as structural cell components so that this increased turnover probably represents a more rapid cell formation and destruction.

The phosphoproteins—chiefly nucleoproteins—are principally cell building blocks. They include desoxyribonucleic acid which is found primarily in the nuclei of cells and is believed to serve an important function in cell division and mitosis⁴. Another phosphoprotein, ribonucleic acid, is a constituent of the cytoplasm and nucleoli and appears to play an integral part in metabolic activity, especially in those cells in which active protein synthesis is occurring. Therefore, the 126% increase in the phosphoprotein turnover observed in gastric cancer probably results from increased tissue synthesis and increased mitotic activity.

The tumor tissues are thus synthesizing phosphoproteins at more than twice the normal rate. Catabolism must also be increased to some extent, since the increased rate of turnover is much higher than the observed rate of growth. These experiments appear to indicate that the increased size of the tumor results from an increased synthesis of cell constituents and an increased breakdown which, however, is not rapid enough to maintain a constant normal size.

An increase of 126% in the phosphoprotein fraction of the gastric tumor does not represent sufficient selective uptake over the normal to permit the localization and detection of tumors by scanning the stomach with a Geiger counter. The normal gastric mucosa is an actively metabolizing tissue in regard to phosphorus and consequently offers little opportunity for a highly selective uptake of radioactivity on the part of the tumor because of the relatively high uptake by the normal mucosa itself.

The possibility suggested itself that the regions in which cancer is common, such as the antrum and lesser curvature of the stomach might have a metabolism more like cancer than did those regions where cancer is rare. No satisfactory explanation has been advanced for the frequency of tumors in the antrum and prepyloric region and the extreme rarity of malignancies of the duodenum a few millimeters away. The rate of phosphorus turnover, however, as well as the phosphorus content of the duodenum, antrum, lesser curvature and greater curvature of the stomach were essentially the same and fell within the normal range.

The clinical observation that cancer of the stomach and atrophic gastritis occur more frequently than would be expected from their occurrence alone in the general population has led to the suggestion that atrophic gastritis might

be a precancerous lesion. If this were true, one might expect that the atrophic mucosa would show chemical or metabolic properties intermediate between the cancer and the normal. Cowdry¹³ observed this to be the case with many properties of experimental and naturally occurring cancers of the skin. To investigate this possibility the uninvolved mucosa of cancer-bearing stomachs (usually showing atrophic gastritis) was compared with the mucosa of non-cancer-bearing stomachs. At least in regard to the rate of turnover of phosphorus, no difference could be observed. The evidence tends to show that the malignant type of metabolism is limited to the confines of the tumor itself, and that the rest of the mucosa behaves normally.

SUMMARY

The rate of turnover of radioactive phosphorus by gastric carcinoma and by the non-cancerous gastric mucosa has been measured in humans and the phosphorus content determined.

1. Gastric carcinoma exhibits a 48.5% higher turnover of phosphorus than the non-cancerous gastric mucosa.

2. The rate of turnover of protein phosphorus was increased 126% in the cancer tissue; the lipid phosphorus turnover was increased 44%. There was no change in the acid soluble fraction.

3. The increased rate of phosphorus turnover is limited to the cancer itself and is not demonstrable in the surrounding tissue.

4. There is no difference in the metabolism of radioactive phosphorus between those areas of the stomach where cancer commonly occurs and those in which it is rare.

5. The atrophic gastric mucosa metabolizes radioactive phosphorus at the same rate as the normal mucosa.

6. The phosphorus content of gastric cancer and the non-cancerous gastric mucosa is essentially the same.

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THE ABSORPTION OF BARIUM SULFATE AND NON-ABSORPTION OF ZIRCONIUM DIOXIDE FROM THE GASTROINTESTINAL TRACT*

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As a result of his studies on the gastrointestinal passage time of barium sulfate and other materials presumed to be inert, Alvarez¹ states "A little barium is apparently absorbed, enough to act as a stimulus to intestinal activity". It is interesting to consider the possibility that for many years roentgenologists have been studying the gastrointestinal tract with the aid of a material which is a stimulant and therefore may not present an entirely normal pattern. When radioactive isotopes became generally available, the opportunity of further testing Alvarez' conclusion was presented. Therefore, barium sulfate containing radioactive Ba^{140} was fed to rats, and because the absorption of definite amounts of Ba was revealed, the experiment was repeated using spectrographic determination of barium in rats which had been fed ordinary $BaSO_4$. As a control, zirconium dioxide, which is believed to be completely insoluble and for which no ionization constant can be found in the literature, was employed using radioactive Zr^{95} as the tracer element. These control studies revealed that the apparent absorption of barium could not be attributed to faulty technique since no absorption of Zr was found and, in addition, certain properties of ZrO_2 came to light which suggested it might have particular virtues as a contrast medium in gastrointestinal tract roentgenology.

METHODS

Ba^{140} (admixed with its radioactive daughter lanthanum¹⁴⁰) was obtained from the Isotopes Branch, United States Atomic Energy Commission, in the form of its soluble acid salts. Radioactivity in this form was mixed with sufficient barium chloride to give the desired quantity when precipitated as the sulfate. The collected sulfate precipitate was then mixed with powdered Rockland rat diet in a ball mill for 24 hours and samples were assayed for radioactivity in order to determine uniformity of admixture of the barium sulfate.

In the first experiment, two adult rats were fed 150 gm. of Rockland diet containing 3.3% of barium sulfate (including 4 millicuries as $Ba^{140}SO_4$) and

* Read at the Annual Meeting of the American Gastroenterological Association, Atlantic City, June 9, 1949.

The barium and zirconium used in this investigation were supplied by the Monsanto Chemical Company on an allocation from the Isotopes Division, U. S. Atomic Energy Commission.

the entire amount was consumed in 5 days. This was followed by one day of normal Rockland rat diet. In the second experiment 30 gm. of diet containing 6.7% of barium sulfate (including 4 millicuries as $\text{Ba}^{140}\text{SO}_4$) was fed to 2 rats, and the entire amount was consumed in 2 days, followed by 2 days of normal diet. At the end of the feeding period the bodies of the animals were scrubbed with soap and water until the radioactivity adhering to the hair was reduced to a low constant value, usually about 10 c/min. for a clipping of hair. Especial care was taken to wash out thoroughly the mouth and ears. Air was then injected subcutaneously until the skin was well separated, and the skin was peeled back from a midline thoracoabdominal incision allowing the least possible contact between hair and subcutaneous tissue. The head, feet, and tail were cut off from the carcass leaving them attached to the skin. The perineal skin was not detached until an abdominal incision was made and the symphysis cut through; the gastrointestinal tract was then removed in toto together with the skin of the perineum. The liver, which had been removed with the gastrointestinal tract, was saved. The eviscerated body, together with the liver, was thoroughly washed in warm tap water until all adhering hairs were removed. This portion of the rat will be referred to as the "carcass". The gastrointestinal tract and perineal skin were discarded, but the remainder of the skin together with head and feet were again washed and placed in a separate dish. They will be referred to as "skin and appendages". These two portions of each rat were then ashed separately in a muffle furnace at not over 600°C. after having first been oven dried at 110°C.

The ash was prepared for determination of radioactivity by a technique which has been found convenient for a variety of radioactive materials. Ash in the amount of 2.5 gm. was weighed out and placed in a shallow, circular, aluminum tray 3.7 cm. in diameter. The tray had previously been placed in a steel die 8 mm. deep. A piece of glassined paper was placed over the opening of the die and a punch, which had been reduced on the outside diameter of its tip in order to fit the tray, was let down on the tray, thus compressing a circle of paper between punch and rat ash powder in the tray. The whole was placed in a Carver laboratory press and the powder in the tray was compressed at 1,000 lbs. per sq. in. The die was then supported on either side by steel bars and slight pressure forced the punch completely through the die, dropping the tray free beneath the die. The wax paper could then be removed from the surface of the powder in the tray without disturbing the powdered ash, and the trays with their contained discs of rat ash powder could be handled without danger of losing any of the sample. If the powder is evenly distributed by hand before compression, the applied pressure produces a uniform thickness and uniform surface which gives highly reproducible geometries.

Measurements of radioactivity were made by placing the samples in Radia-

tion Counter Laboratories sample holders beneath end mica window Geiger tubes using a Nuclear Instrument and Chemical Corporation scaler. Standards were prepared by taking 3 mg. weighed samples of the original BaSO_4 precipitate and diluting serially with ash from normal rats until a 2.5 gm. sample gave a conveniently determinable amount of radioactivity. All readings were corrected for background and resolving time. No corrections for geometry or absorption loss were necessary since both sample and standard were compared under identical conditions.

In all radioactivity measurements the uranium acetate standard was read at frequent intervals in order to determine variations in Geiger tube efficiency. All values were then corrected by the percent by which the uranium standard departed from its average.

In the experiments on the absorption of zirconium from zirconium dioxide, the tracer used was Zr^{95} obtained (together with its radioactive daughter columbium⁹⁵) in the form of the hydroxide. This was converted to the dioxide by heating for 14 hours at 700°C . Then 8.2 mc. of the Zr^{95}O_2 (with its Cb^{95} daughter) were mixed with 15 gm. of commercial ZrO_2 and ball-milled with 400 gm. of powdered Rockland rat diet for 24 hours. At the end of this period, samples showed uniform distribution of radioactivity. Five rats were fed *ad libitum* with this mixture and consumed essentially all of it in 5 days. Two of these rats were then fed a normal diet for 24 hours, 2 for 48 hours, and the remaining rat for 24 days. At the end of these periods, the rats were killed with ether and were treated as described for the rats fed BaSO_4 . Samples of the ash were also prepared as for the barium sulfate-fed samples except that 3.0 gm. of ash were used instead of 2.5. Zr^{95} standards were prepared by dilution of the original material in rat ash and compression of a 3 gm. sample giving suitable activity in an aluminum tray in the usual manner.

When it was found that the technique was successful in that the absorption of barium could be demonstrated whereas there was no detectable absorption of zirconium, 5 rats were fed 5% BaSO_4 in powdered Rockland rat diet for 23 days, the carcasses prepared as described above, and the carcass ash was submitted to Dr. D. L. Timma of Ohio State University, who kindly carried out spectrographic analysis of the ash.

RESULTS

Small samples of skeletal muscle, liver, and bladder urine taken from the animals and read by placing directly in trays without ashing, gave unexpectedly high activity in both the BaSO_4 and ZrO_2 fed rats. Identification of the isotopes responsible for this activity was made in both instances by means of absorption curves using aluminum foil weighing 3.3 mg./cm^2 , and by half-life determinations. Chemical separations were carried out on the excess ash

from the zirconium-fed rats in order to provide additional certainty of identification.

On the ash from the barium-fed rats, absorption curves were complex, as might be expected for the numerous beta and gamma energies emitted by Ba^{140} and its daughter La^{140} , and these absorption curves could not be differentiated with certainty from curves made on the standard samples of Ba^{140} - La^{140} mixture. There was obviously a rapidly decaying component which manifested itself for as long as 36 days and the remainder showed exponential decay corresponding to a half-life of 55 days. Absorption measurements repeated at this time revealed beta ray energies in the neighborhood of 1.5 Mev. The combination of 55 day half-life and 1.5 Mev. beta emission was considered to identify the presence of strontium⁸⁹ as a contaminant in the rat ash. Since it is difficult to make a complete chemical separation of Ba and Sr, it is not surprising that the Ba^{140} received from Oak Ridge contained a small amount of Sr^{89} as a contaminant. The amount of Sr^{89} in the original material was insignificant for ordinary purposes as shown by the fact that decay curves on the original Ba^{140} agreed within the limits of error with the 12.8 day half-life of Ba^{140} . However, there was sufficient Sr^{89} in the material as received so that when fed to rats, it accounted for about 1,000 to 3,000 c/min. in a 2.5 gm. sample of rat ash under our conditions of measurement. Approximately 0.0003% of the total activity fed was found in the carcasses, and 80% of this was present as Sr^{89} .

The more rapidly decaying component was estimated by extrapolating the exponential curve of decay obtained between the 36th and 116th days back to zero, and subtracting this extrapolated curve from the readings actually found during the first four to five weeks, which gave the excess radioactivity over and above that due to Sr^{89} . When plotted on semi-logarithmic paper these values gave half lives of between 10.8 and 13.5 days with an average 12.2 days which is considered as satisfactory error in consideration of the fact that the Ba^{140} activity in the ash was only a small proportion of that due to the Sr^{89} .

The original reading at zero days, corrected for the amount of Sr^{89} present, was then taken as indicating the amount of Ba^{140} which had been absorbed from the BaSO_4 administered, and the amount present in the ash was determined by comparing the Ba^{140} counts attributable to the ash with the Ba^{140} standard made up in rat ash and also read on the zero day.

There is some question as to the accuracy of the determinations on skin and appendages since it is known that a small but definite residual contamination was present on the hair even after thorough washing. Therefore, in table 1 the amount of Ba (as the sulfate) present in the entire rat was calculated on the basis of the concentration present in the carcass only, although

the skin and appendage values are also shown. There is reasonably good agreement between actual Ba^{140} found in combined carcass and skin and appendages with that calculated on carcass basis except for rat 2 in the second group, in which case contamination of the skin and appendages was obviously excessive.

No La^{140} in excess of the amount in equilibrium with its parent Ba^{140} was present in the ash of carcass, or of skin and appendages, since the half-life determinations agreed with the value for Ba^{140} within the limits of error of the method. This indicates that not more than 2 or 3 times the equilibrium

TABLE 1
Absorption of BaSO_4

	mg BaSO ₄		CALC. FOR WHOLE RAT ON BASIS OF CARCASS
	In carcass	In skin and ap- pendages	
I. Rats fed Ba ¹⁴⁰ SO ₄ as 3.3% of diet for 5 days, then 1 day normal diet			
Rat 1.....	0.042	0.030	0.068
Rat 2.....	0.052	0.038	0.090
II. Rats fed Ba ¹⁴⁰ SO ₄ as 6.7% of diet for 2 days, then 2 days normal diet			
Rat 1.....	0.024	0.032	0.041
Rat 2.....	0.032	0.052	0.056

TABLE 2

BaSO_4 present, by spectrographic analysis, in carcass ash of rats fed BaSO_4 as 5% of diet for 23 days

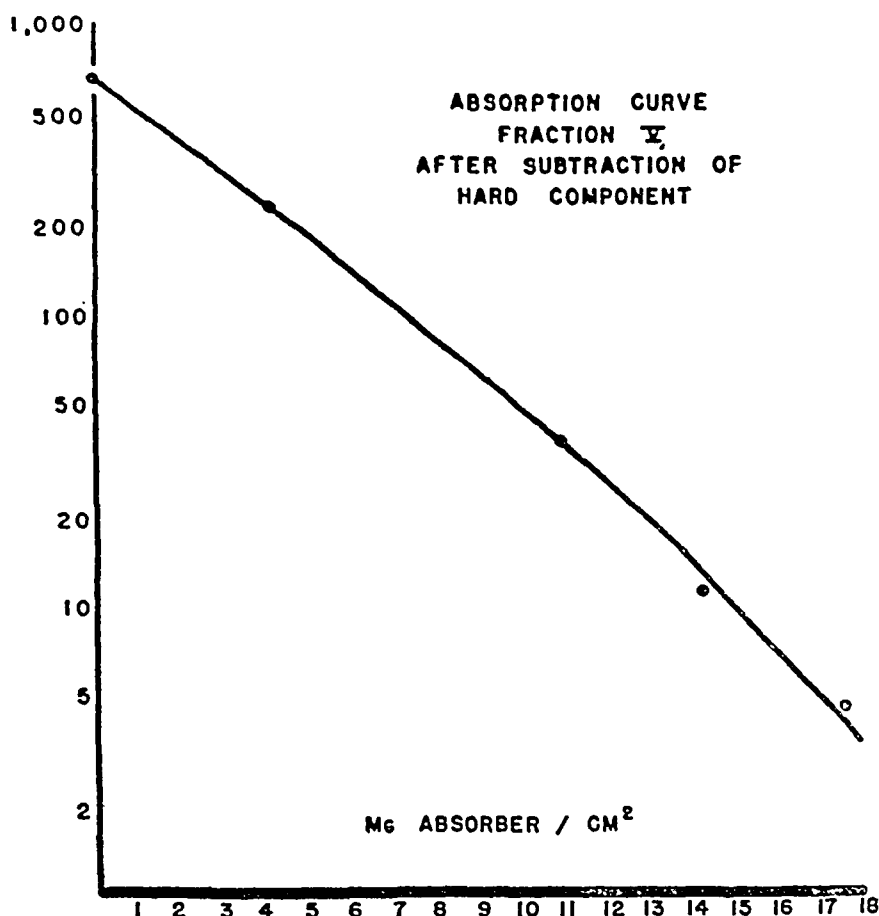
Rat 1.....	0.111 mg
Rat 2.....	0.075 mg
Rat 3.....	0.102 mg
Rat 5.....	0.108 mg
Rat 6.....	0.066 mg

amount could have been absorbed, since a greater quantity would not have decayed during the one week required for feeding normal diet, ashing, and preparing the samples.

The data on the spectrographic determination of Ba in the rats fed BaSO_4 at 5% of the diet for 23 days are given in table 2. The amounts absorbed are more than 3 times as great as those found in the rats fed labeled BaSO_4 for 2 days, and about twice as great as the amounts in rats fed labeled BaSO_4 for 5 days. Apparently the amount of Ba absorbed is principally influenced by the duration of feeding rather than by the amount of BaSO_4 in the diet.

When the ash from the zirconium-fed rats was studied, the rate of decay

was less than that of the 65-day Zr^{95} and absorption curve studies showed a weak component present in small quantity with a high (approximately 1.7 Mev.) beta emission as the predominant activity. Since the contaminant in this instance appeared to correspond to the 14.3 day, 1.69 Mev., phosphorus³², chemical fractionation was carried out on this assumption. Of the



[FIG. 1. Absorption curve of fraction 5 (major residue after precipitation of phosphorus and calcium from rat ash). The hard (gamma ray) component has been subtracted. The smoothness of the curve indicates the presence of only columbium⁹⁵.

excess ash from rats 1 and 2, 3.5 gm. were dissolved in nitric acid and the phosphate precipitated as the molybdate. This precipitate was dissolved in ammonium citrate mixture and reprecipitated as magnesium ammonium phosphate, 2.5 gm. of precipitate being obtained. This precipitate was compressed in the usual manner in an aluminum tray and it was found that its half-life was 14.5 days with a beta ray energy of approximately 1.7 Mev. No other activity except that of P^{32} was indicated by absorption curves or half-life measurements in this precipitate and the identification of P^{32} as the contaminant was considered to be complete.

Further fractionations* were carried out in order to concentrate any Zr^{95} or its Cb^{95} daughter which might be present. The filtrate from the phosphate precipitate was acidified and evaporated and the precipitate which occurred on evaporation (presumably molybdic acid) exhibited no activity. The filtrate was then treated with ammonium oxalate to precipitate calcium and the filtrate from the calcium precipitate was evaporated to dryness. The dried residue was extracted repeatedly with hot HCl and the acid extracts evaporated. This showed an activity of 248 c/min. and an absorption curve (fig. 1) indicated a beta component with energy certainly less than 0.2 Mev. together with a gamma component. This activity could not be attributed to Zr^{95} which has a beta ray energy of 0.394 Mev., and is believed to indicate the absorption of small amounts of the Cb^{95} daughter. Extraction with hydrofluoric acid of the residue left after the hydrochloric acid extraction (fraction 6) gave 9

TABLE 3

3.5 g carcass ash from rats 1 and 2 fractionated and activity of fractions determined 20 days after beginning Zr^{95} feeding

FRACTION	CHARACTER OF FRACTION	COUNTS/ MIN.
I	Mg $NH_4PO_4 \cdot 6H_2O$	622
II	Evaporated filtrates from I	8
III	Precipitate formed on concentration of filtrate from molybdate precipitation	0
IV	Calcium oxalate precipitated from molybdate filtrate	0
V	Evaporated filtrate from IV extracted with hot HCl and extract evaporated	248
VI	Residue not extracted in V	9

c/min. on evaporation. It will be noted that substantially all the activity is concentrated in fractions 1 and 5, and absorption curves and half-life measurements on these two fractions indicated that they contained no isotopes except P^{32} and Cb^{95} , respectively. Two layers of foil reduced the number 6 fraction to background level and the 9 c/min. in this fraction are therefore presumably Cb^{95} . The activity of fraction 2 was not reduced by 30.5 mg./cm.² of absorber and the 8 c/min. in this fraction cannot therefore be zirconium, thus there is no evidence for the presence of zirconium in any of the chemically separated fractions of the ash. A summary of the activities obtained in the various chemical fractions is presented in table 3.

Absorption curves were made on each of the rat ash samples with the exception of the ash of skin and appendages from rat 3 which was lost. Table 4 presents for each sample of ash the total counts, counts attributable to P^{32}

* The author wishes to thank Dr. Otto Ungnade for carrying out the chemical fractionations.

and counts attributable to Cb^{95} . These counts are all extrapolated to zero absorber; half absorption values for P^{32} and Cb^{95} determined from these

TABLE 4

Total c/m, c/m attributable to P^{32} , and c/m attributable to Cb^{95} , all extrapolated to zero absorber.
Half absorption values ($\mu\frac{1}{2}$) given for P^{32} and Cb^{95} beta rays

ASH	DAYS AFTER FEEDING BEGUN	TOTAL	P^{32}	Cb^{95}	$\text{P}^{32} \mu\frac{1}{2}$	$\text{Cb}^{95} \mu\frac{1}{2}$
		c/m	c/m	c/m	mg/cm ²	mg/cm ²
C ₁	11	1,000	820	180	86	6.5
C ₂	10	980	810	170	92	5.8
C ₃	21	630	540	90	88	4.5
C ₄	21	1,320	1,220	100	91	4.0
C ₅	34	210	180	30	75	5.0
S ₁	14	790	650	140	92	4.5
S ₂	20	420	375	45	95	5.0
S ₄	19	980	902	78	91	4.0
S ₅	35	160	132	28	78	4.8
Average.....					87.6	4.9

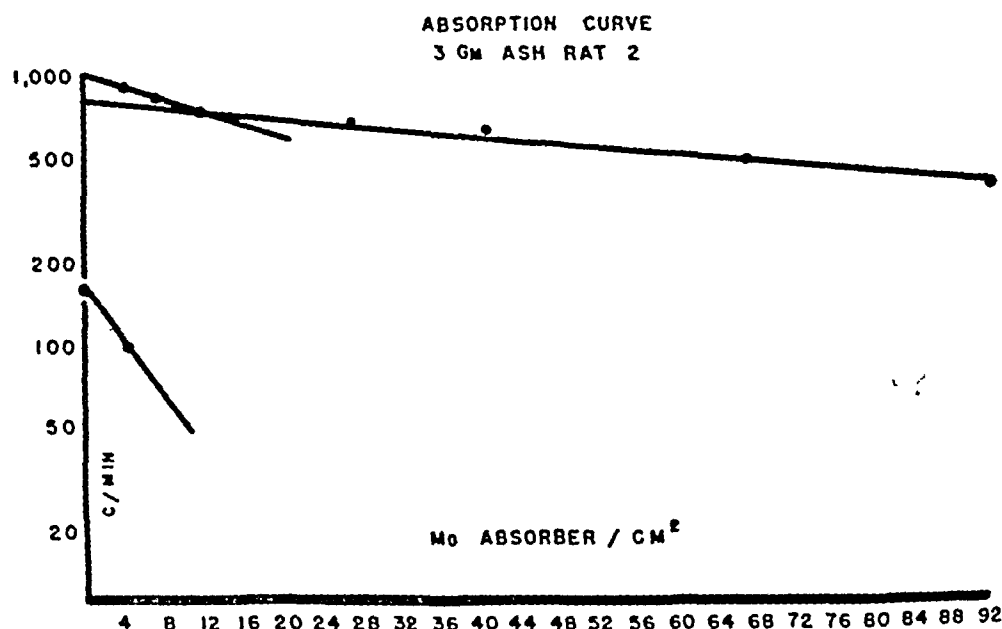


Fig. 2. Absorption curve on 3 gm. of ash from the carcass of rat 2 in the zirconium series. The upper curve shows all points obtained out to 92 mg. of absorber per cm.² and lines are drawn through the points for both hard and soft components. The lower curve shows the soft component after subtraction of hard component values. Half absorption value for the hard component (phosphorus³²) is 92 mg./cm.² and for the soft component (phosphorus³²) is 5.8 mg./cm.².

curves are also presented in table 4, the values being obtained from absorption curves of the type shown in figure 2. Cb^{95} absorption curves were obtained

by subtracting the hard P^{32} component which was extrapolated to zero. By using aluminum foil weighing 3.3 mg./cm.², only 2 points were available on which to base Cb^{95} absorption curves since 2 layers of foil gave complete absorption of the weak Cb^{95} beta ray. Therefore the variability in the Cb^{95} absorption curves is not surprising. However, in none of these absorption curves was there any indication of any component other than Cb^{95} or P^{32} or, in other words, no beta rays with an energy in the neighborhood of 0.4 Mev. (corresponding to Zr^{95}) were detected. On the basis of the data given by Bale² the average value of 87.6 mg./cm.² for P^{32} component would represent an energy of 1.66 Mev. while the value of 4.9 mg./cm.² for Cb^{95} rays would fall well below 0.2 Mev. Such comparisons can only be approximate in view of the differences in geometry and in thickness of sample between our condi-

TABLE 5
Half lives of P^{32} and Cb^{95} as determined on 4 samples of rat carcass ash

SAMPLE	HALF-LIFE	
	P^{32}	Cb^{95}
	days	days
C ₁	14.8	32.3
C ₂	15.0	42.6
C ₃	14.0	40.0
C ₄	14.3	22.0
Average.....	14.5	34.2
True T $\frac{1}{2}$ P^{32}	14.3	Cb^{95}35.0

tions and those of Bale, but permit the conclusion that only P^{32} and Cb^{95} were present and that no Zr^{95} could be detected.

To further complete the identification of the radioactive materials present, half-life determinations on the hard (presumably P^{32}) and soft (presumably Cb^{95}) components in each rat ash were made, all values being corrected to air and window absorber (4.1 mg./cm.²) and the Cb^{95} value being calculated by subtraction of the P^{32} value from the total. Since the Cb^{95} values in most instances represented 8 to 10% of the total counts, the determination of the Cb^{95} half-life was subject to a high degree of error. These P^{32} and Cb^{95} half-life estimations are presented in table 5. The value of 14.5 days for P^{32} is in good agreement with the true value of 14.3 days but the variation in individual determinations for Cb^{95} is almost 100% and it is accidental that the average value of 34.2 days comes close to the true value of 35 days. However, none of the values obtained for Cb^{95} are compatible with the 65 day half-life of Zr^{95} and confirm the absence of any activity which might be attributed to this latter isotope.

An average of 0.01% of the total activity fed as $\text{Zr}^{95}\text{-Cb}^{95}$ was found in the carcasses, and at least 90% of this activity was in the form of P^{32} .

Since attempts to detect Zr^{95} included determinations of half-life, absorption studies, and chemical fractionation followed by half-life determinations and absorption studies, it is believed that no more than 5 counts/min./sample of ash could have gone undetected. This would correspond to 0.002 mg. of ZrO_2 .

DISCUSSION

Since the solubility of barium sulfate at body temperature is 0.25 mg./100 ml. of water it is not surprising that measurable amounts of barium should be absorbed when BaSO_4 is given by mouth. The actual amounts found in the body probably do not represent the total quantity absorbed since Chaikoff, Fisher and Entenman³ have found that parenterally administered barium is rapidly eliminated during the first 4 days, about 30% being excreted by the gastrointestinal tract during the first 24 hours. The urinary excretion of barium appears to be slight and that which is not eliminated in the feces is stored principally in the bone. The present figures for barium content of the body in the barium sulfate fed rat probably indicate chiefly the quantity stored in bone and considerably more than this amount may be presumed to have passed through the gastrointestinal tract from its lumen to the tissues of the body during the process of absorption. Sollmann⁴ states that 3.0 mg. of BaCl_2 per kilo given intravenously are purgative in dogs. The amounts absorbed by the animals in this series are from about 0.3 to 0.7 mg. of BaSO_4 per kilo or $\frac{1}{10}$ to $\frac{1}{5}$ of the amount of barium which when given by vein causes pronounced activity of the gastrointestinal tract. It seems reasonable to conclude that passage from gastrointestinal tract lumen to blood of the quantities of barium absorbed by rats in this series might have some effect upon gastrointestinal motility. Whatever pharmacological effect may be produced does not appear to result in actual toxic manifestations since Free⁵ has shown that chronic administration of barium sulfate to rats over a period of 80 days has no effect upon rate of growth or fertility when the barium sulfate is given in a dosage of 100 mg. suspended in 3 ml. of water 5 times per week by stomach tube.

It should be noted that the 0.002 mg. of ZrO_2 which could have been present in carcass ash without detection is only 4.3% of the amount of BaSO_4 present in the carcasses of the group I BaSO_4 fed rats, in which the duration of feeding was also 5 days. This quantity of ZrO_2 of course represents the maximum which could have escaped detection and there is actually no evidence of the absorption of any ZrO_2 .

NOTE ON THE PROPERTIES OF ZIRCONIUM DIOXIDE AS A ROENTGENOLOGIC CONTRAST MEDIUM

The failure of any detectable ZrO_2 to be absorbed led us to investigate its potentialities as a useful radiopaque material. A search of the literature reveals that Kaestle^{6, 7} used ZrO_2 in 1909; the fact that until recently ZrO_2 has been excessively expensive may account for the absence of subsequent studies on this material.

Free⁵ has further found no toxic effects from the intravenous administration of 100 mg. of sodium zirconium lactate per kilo, and only a slight temporary growth suppression of 150 mg. Even the soluble salts of zirconium are therefore nontoxic as compared to barium.

In spite of its lower molecular weight, Zr has a higher absorption coefficient for roentgen rays at most of the wave lengths employed in roentgenology

TABLE 6
Comparative radiopacities of $BaSO_4$ and ZrO_2

VOLTAGE AND FILTRATION	RATIO OF OPACITY OF ZrO_2 TO $BaSO_4$
40 Kv 1 mm Al	3.0
60 Kv 1 mm Al	1.8
75 Kv 1 mm Al	1.5
90 Kv 1 mm Al	1.15
40 Kv 6 mm Al, 0.25 mm Cu	2.5
60 Kv 6 mm Al, 0.25 mm Cu	1.1
75 Kv 6 mm Al, 0.25 mm Cu	1.0
90 Kv 6 mm Al, 0.25 mm Cu	0.9

than does Ba due to the lesser stability of the electrons in its K shell which absorb roentgen ray quanta at longer wave lengths than do the K electrons of barium. In addition, the two oxygen atoms of ZrO_2 constitute a smaller "non absorbing fraction" of the total molecule than the sulfate group in $BaSO_4$.

The absorption of roentgen rays by ZrO_2 as compared with $BaSO_4$ was therefore studied by placing suspensions of these two agents in cups and exposing them at various wave lengths followed by measurements of the film blackening beneath the suspensions. Data from the results obtained are presented in table 6 and show that except at the highest voltages now in common use ZrO_2 is superior to $BaSO_4$ in absorptive capacity. This would probably not be a major consideration in actual practice since absorption can be made satisfactory by selecting the proper quantity of radiopaque material and need not be a limiting factor in the use of either substance.

A more important property of ZrO_2 , however, is the smaller degree of roent-

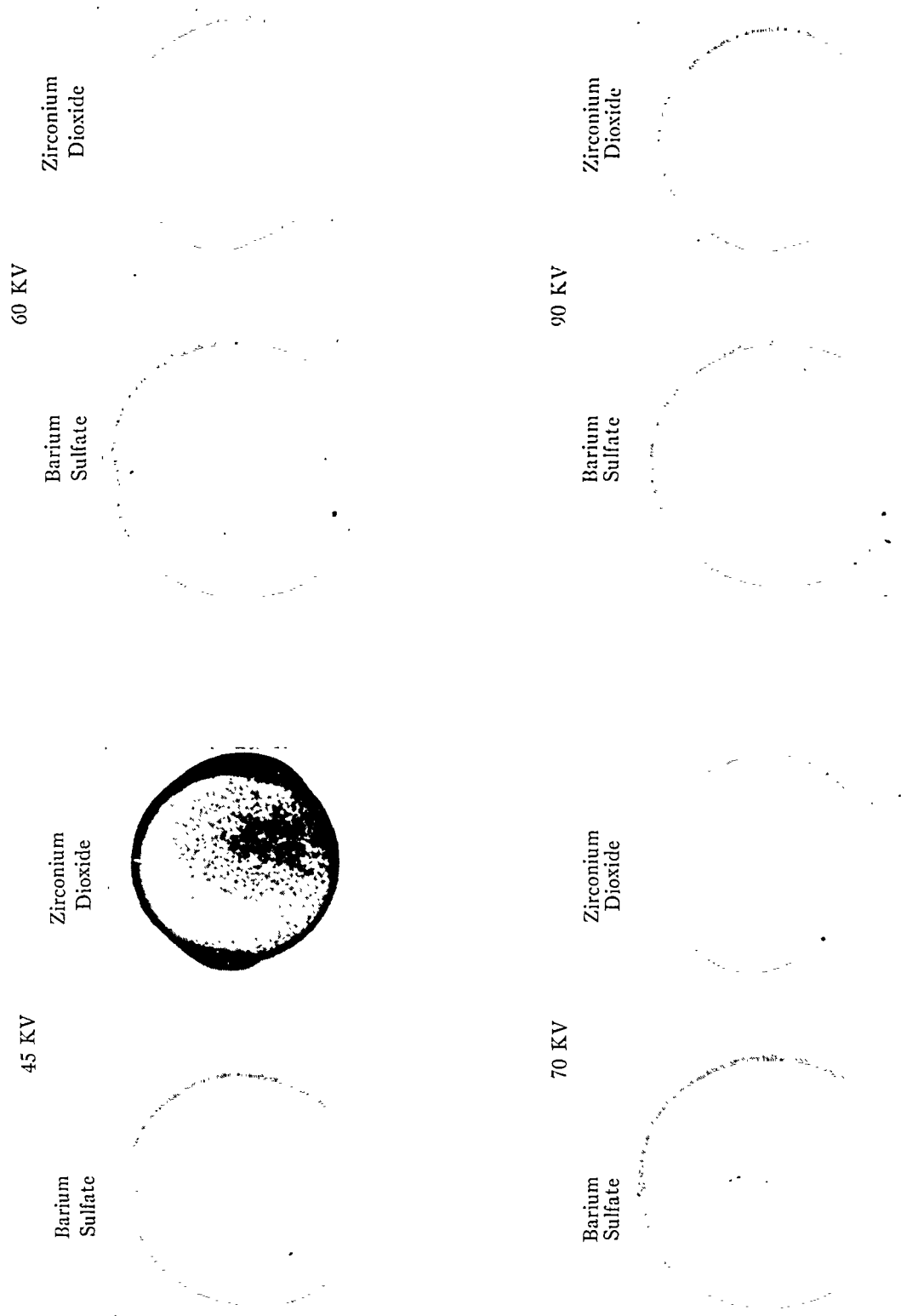


FIG. 3. Comparison of roentgen ray scattering effects of barium sulfate and zirconium dioxide at various voltages. All exposures made on tablets 26 mm. in diameter containing 2.73 gm. of radiopaque material, tablets being placed in openings in lead shield. Sufficient exposure used to penetrate radiopaque material except that greater radiopacity of ZrO_2 prevents complete penetration at 45 Kv. Larger *apparent* diameters and fuzziness of outlines of $BaSO_4$ tablets are due to greater scattering.

gen ray scattering produced by this substance as compared with BaSO_4 . This was observed when the tests mentioned above were made, and additional studies of scattering were carried out by producing thin tablets containing 2.73 gm. of either BaSO_4 or ZrO_2 and 0.27 gm. of gum acacia. These tablets were 2.5 cm. in diameter. They were exposed by placing them in a lead shield which had two rows of circular openings which would just admit the tablets. Exposures were made at 45, 60, 75, and 90 kilovolts using a 36-inch distance and 100 milliamperes of current. Figure 3 illustrates the greater scattering produced by BaSO_4 as compared with ZrO_2 and the excess radius of blackening (which may be taken as an index of scattering) for the two materials is given in table 7.

TABLE 7
Comparative roentgen ray scattering by BaSO_4 and ZrO_2

EXPOSURE	INCREASE IN DIAM. DUE TO SCATTERING (MM.)	
	BaSO_4	ZrO_2
45 Kv		
3.25 sec.....	0.5	0.0
7.0 sec.....	0.8	0.05
60 Kv		
1.5 sec.....	0.8	0.2
3.0 sec.....	1.1	0.4
75 Kv		
0.6 sec.....	1.1	0.3
1.5 sec.....	1.3	0.6
90 Kv		
0.2 sec.....	1.0	0.25
0.4 sec.....	1.3	0.7

Therefore the lack of toxicity, equal or superior absorbing power, and reduced degree of scattering suggest that in spite of its greater cost ZrO_2 may be superior to BaSO_4 as a contrast medium for roentgenologic studies of the gastrointestinal tract. Clinical trials of ZrO_2 are now being carried out.

SUMMARY

The absorption of barium after the oral administration of barium sulfate to rats was demonstrated by the administration of radioactive Ba^{133} as a tracer followed by determination of the radioactivity of the rat carcass ash, and was confirmed by the spectrographic determination of barium in carcass ash of rats fed ordinary BaSO_4 . Control studies using zirconium dioxide indicated that no detectable amount of the latter material was absorbed, indicating that the apparent absorption of barium could not be attributed to faulty technique.

Certain properties of zirconium dioxide which invite consideration of its use in roentgenologic investigations of the gastrointestinal tract are discussed.

The author wishes to express his appreciation to Dr. R. R. Williams of Notre Dame University for his helpful advice on the techniques of radioactive isotope determination, and the interpretation of the results.

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DISCUSSION OF PAPERS BY E. C. REIFENSTEIN ET AL., S. J. GRAY
ET AL., AND L. A. CRANDALL, JR.

DR. LEON SCHIFF (Cincinnati, Ohio): I should like to ask Dr. Reifenstein two questions: Has he observed any relationship between these abnormal steroids and the gastric acidity in patients with cancer, and has he observed their production in achlorhydria unassociated with gastric cancer?

I was very much interested in Dr. Gray's observation of no difference in the turnover of radioactive phosphorus in the presence of gastric atrophy. We noticed no difference in the excretion of radio-iodine by the stomach in the presence of gastric atrophy.

I should like to ask Dr. Gray if he has made observations at shorter intervals than thirty-six hours in order to approximate more closely true turnover of radioactive phosphorus.

DR. EDWARD C. REIFENSTEIN [New York, N. Y.]: I am afraid I can't answer either of the questions Dr. Schiff raised.

I think we have data, although we have not analyzed it, in regard to the response in patients with achlorhydria without gastric cancer.

DR. SEYMOUR J. GRAY (Boston, Mass.): The atrophic gastric mucosa is somewhat cellular because of an increase in lymphocytes as well as plasma cells, and this may explain why the radioactive uptake of atrophic mucosa does not differ from the normal.

In regard to the uptake at various intervals of time, we have varied the time between twenty-four and forty hours after the injection of the radioactive phosphorus. The uptake at twenty-four hours is essentially the same as that at the end of forty hours. Theoretically if one were to take a sample very shortly after injection, the specific activity might be somewhat higher. This can be done with brain tumors, for example, where one can take small pieces of brain tissue at various intervals and study the uptake. The uptake is increased somewhat for the first few hours, but the thirty-six-hour level usually is quite representative.

OBSERVATIONS ON A PATIENT WITH PANCREATIC FISTULA

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INTRODUCTION

The purpose of this presentation is to describe our observations on a patient with an external pancreatic fistula. The opportunity to observe a complete external pancreatic fistula in a human occurred following a surgical procedure. This study was carried on over a period of three months during which time the patient was in excellent condition.

CASE REPORT

This 56 year old white male entered the hospital with a history of intermittent jaundice and right upper quadrant pain. At the time of exploratory laparotomy a carcinoma of the ampulla invading the common duct was found and a resection of the duodenum from the pancreas was performed. On the third postoperative day a bulging of the apex of the wound occurred which ruptured spontaneously, releasing several hundred cc. of clear watery fluid, strongly alkaline, chemically identified as pancreatic fluid. At autopsy 6 months later the dissection of the external pancreatic fistula revealed that it had its origin from the ampulla of Wirsung, confirming the existence of a complete pancreatic fistula.

TECHNIQUE

The collection of pancreatic fluid from the fistula was accomplished by placing a small French catheter (#16) in the mouth of the fistula and connecting it to a continuous water aspirator with a collecting trap to catch the fluid. This method was simple and efficient, preventing spillage of pancreatic enzymes over the anterior abdominal wall and digestion of the fistulous area. All samples were collected and measured at fifteen minute intervals. The fluid collected was stored in an ice chest. All results are expressed in terms of volume flow (cc.) per fifteen minutes.

During the period of observation precautions were taken to maintain the patient in electrolytic balance besides providing a well-balanced and calorically adequate diet with supplementary vitamins. The patient was trained to pass his own Levine tube and instill into his stomach the daily collections of pancreatic fluid, thus helping to keep an adequate fluid intake.

METHODS AND DISCUSSION

Observations on the rate of flow under the following conditions were made:

1. Diurnal and nocturnal pancreatic secretions.

* Read at the Annual Meeting of American Gastroenterological Association, Atlantic City, June 9, 1949.

2. Influence of diet.
3. Psychic phase.
4. Drugs and intravenous fluids.

Diurnal and Nocturnal Pancreatic Secretions

The first objective was to determine the rate of flow during the day and night. For a period of several days all precautions were taken to standardize the patient's environment. A series of fixed meals were presented by the same person at approximately the same time. All undue psychic influences were eliminated.

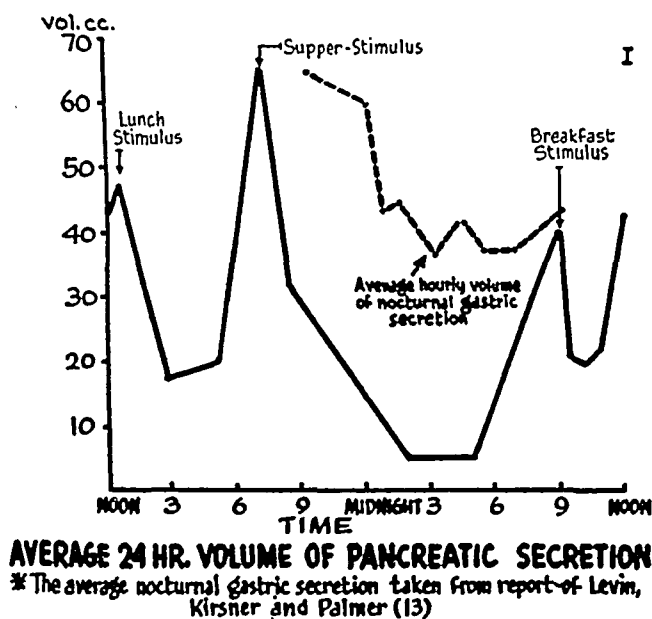


CHART 1

The daily 24 hour volume averaged 1250 cc. during this period. The figures for the total 24 hour volume compare satisfactorily with those of other investigators^{1, 2, 3, 4, 5, 6, 7, 8}. Miller⁹ observed a daily flow of 1.7 liters. In his case the fat content of the patient's stool was within normal limits from which fact he concluded that some pancreatic secretions were going into the duodenum. If this were true one would expect a higher daily total volume than we observed. Dreiling¹, Lagerlöf², Lake⁵, and Diamond⁴ studied pancreatic secretion in the human by the duodenal drainage method. Each observer obtained similar results with a range of 100-450 cc. per 80 minute period.

Chart 1 illustrates the difference in the pancreatic secretory rate during

the day and night. We see that the secretion diminishes fairly rapidly after the evening meal, and reaches its lowest rate of flow between 2 and 4 A.M., 4.7 cc. per fifteen minute interval as compared to the secretions between 2 and 4 P.M. of 15 to 20 cc. for an equivalent time.

The peak of the daily secretion occurred after the heaviest meal which was usually the supper feeding. The maximum rate obtained was 60 to 70 cc. per fifteen minute period. Although the other two feedings (breakfast and lunch) did not induce such a high level of secretion all three feedings initiated some acceleration of the rate of flow. Within ninety minutes after each meal the maximum rate was obtained and by the end of 22 hours the basal rate for that period of the day was restored.

Influence of Diet

The introduction of various foodstuffs into the stomach was thoroughly studied by Miller⁸ and Comfort⁷. Based on their methods we ran comparable tests. With the aid of a thin Levine tube various types of food substances were placed in the stomach. We used carbohydrate in the form of 100 cc. of 50% glucose; fat in the form of 100 cc. of pure olive oil and protein as a 25% solution of gelatin.

Each afternoon after the basal secretion had been obtained with a Levine tube in place, one of these substances was introduced into the stomach. The results given are the average figures for five separate tests run with each substance:

Carbohydrates and proteins cause practically the same stimulation in the rates of pancreatic secretion, carbohydrates causing a maximum flow in about one hour with a rate of 40 cc. per fifteen minute period and protein giving a response of 36 cc. After both carbohydrate and protein the secretory rate returned to basal within 90 minutes. Olive oil produced a small response which slowly reached a peak of 25 cc. per 15 minute interval lasting for 90 minutes, then slowly decreasing. This is demonstrated in Chart 2.

Miller and Wiper reported only a slight alteration of pancreatic secretions using olive oil while carbohydrate and protein gave more response. The findings were also confirmed by Comfort et al.⁷ and McCoughan^{6, 9}.

Psychic Phase

One afternoon while eating, the patient was told he had to drink his pancreatic secretions. Prior to this he was taking all secretions by intubation. This information was so upsetting that the patient stopped eating. Simultaneously the pancreatic secretions rapidly decreased and within one-half hour the flow was reduced from 32 cc. to 10 cc. per fifteen minute interval.

For several days a special select meal was discussed with the patient. When

the patient was finally confronted with this select meal he was not allowed to eat it for a period of fifteen minutes. When the patient attempted to eat the meal was quickly removed and a substitute feeding was presented. The results are seen in Chart 3. The flow during this period was in the form of a biphasic curve, one peak representing the anticipated meal followed with a rapid decline when the meal was removed, and then a slow rise when the substitute meal was presented.

Drugs and Intravenous Fluids

Two drugs were employed in an attempt to decrease the pancreatic secretions, atropine and dihydroergotamine (D.H.E.-45). These drugs were given

EFFECT OF CARBOHYDRATE FAT AND PROTEIN ON PANCREATIC SECRETION

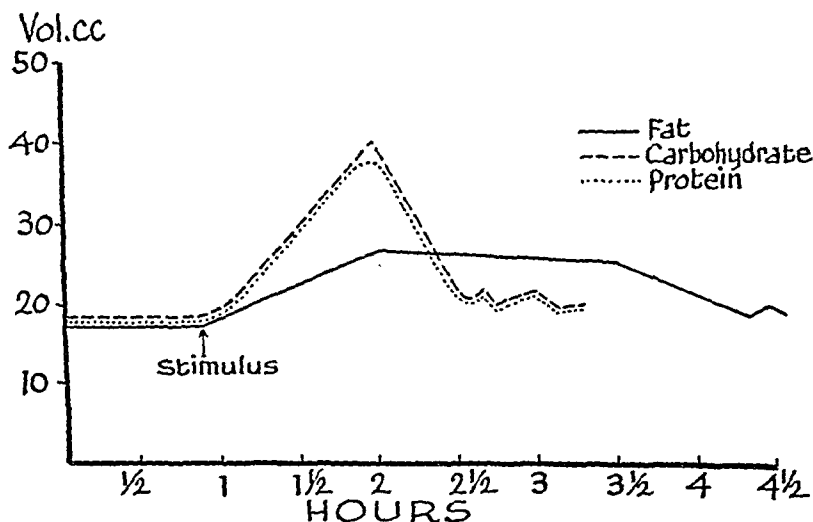


CHART 2

between two and four A.M. at a time of the greatest depression of the normal pancreatic secretion (4.7 cc. per fifteen minute interval).

When 1.0 mg. of atropine was given intramuscularly there followed a rapid reduction of the pancreatic secretion with a rapid return to the basal rate in one hour. Dihydroergotamine (1.0 mg. intramuscularly) given under similar conditions produced a slow reduction of pancreatic flow, maintaining this reduced level for practically two hours, and then returning to the basal level (Chart 4). D.H.E. 45 and atropine produced the same reduction of the volume flow to 2.7 cc. for a fifteen minute interval. No additive effect was found when atropine was administered followed by D.H.E. 45 at a half hour interval.

SHAM FEEDING AND EFFECT ON PANCREATIC SECRETION III

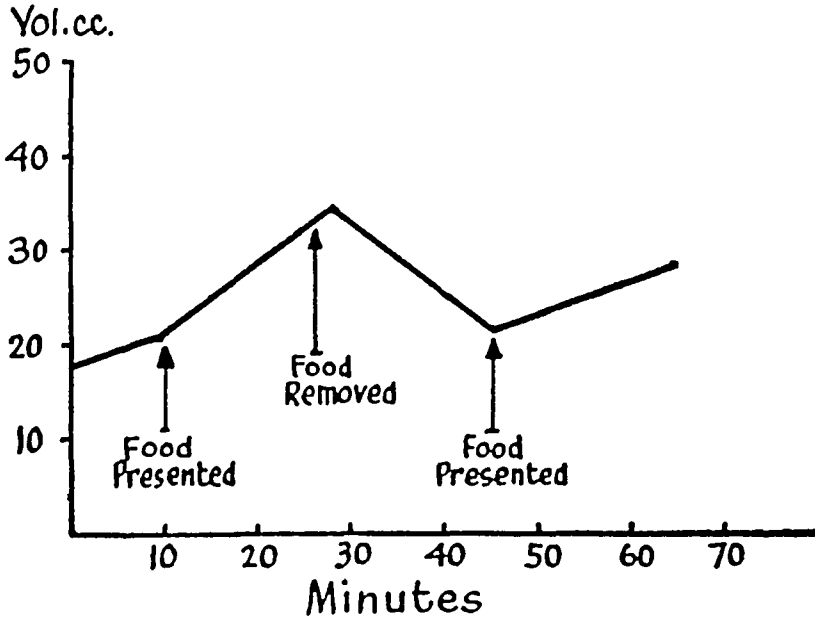


CHART 3

EFFECT OF ATROPINE-SULFATE 1MG AND DIHYDROERGOTAMINE 1MG ON PANCREATIC SECRETION AT NIGHT IV

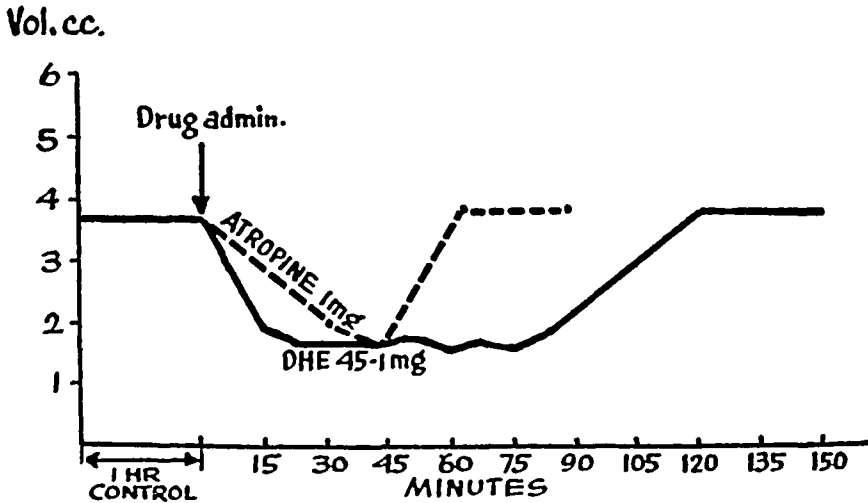


CHART 4

In experiments on dogs D.H.E. 45 has been shown to be capable of inhibiting the secretory response to secretin¹². Although the effect of atropine on secretin

stimulated secretion has been variously reported¹⁰, in a recent study Thomas and Crider found a definite inhibition¹¹.

Intravenous infusion of various physiological solutions caused an augmentation of the total pancreatic volume. Saline in five or ten per cent glucose solution gave similar results while saline alone gave a slightly lower response. The afternoon basal secretion of 17 cc. for fifteen minute period was elevated to 28-31 cc. and maintained during the period of infusion. This, too, confirmed the findings of Miller, et al.⁸

SUMMARY

1. A case of a complete external pancreatic fistula is reported with physiological observations of the rate of secretion under various conditions. All experimental procedures were reported in the terms of rate of secretion for 15 minute intervals. Figures presented are the averages obtained during the extended observation period.

2. Diurnal and nocturnal pancreatic flow were observed for three months. A maximum rate of 60-70 cc. for fifteen minute interval occurred after the largest meal of the day and the lowest rate of secretion, 4.7 cc., occurred between 2 and 4 A.M. The secretagogue effect of gastric gavage of carbohydrate, fat and protein were noted. Carbohydrate and protein gave similar responses while fat in the form of olive oil produced a slow rise not reaching the height produced by carbohydrate and protein but lasting longer.

3. The sight of a tasty meal was found to produce an enhanced pancreatic volume which did not reach the rate of flow seen when the patient was allowed to ingest food. Emotional distress decreased pancreatic secretion.

4. Diminution of pancreatic secretion was accomplished with the use of two drugs, dihydroergotamine and atropine, producing a depression to 2.7 cc. per fifteen minute interval. Intravenous infusion of saline with glucose accelerated the rate of flow more than saline alone.

5. Nocturnal secretion of the pancreas appears to follow a pattern similar to that seen in the human stomach.

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DISCUSSION

DR. J. EARL THOMAS (Philadelphia, Pa.): One of the difficulties involved in interpreting experiments of this sort on any human subject is the fact that pancreatic secretion is closely tied up, through the secretion mechanism, with the gastric secretion, so that unless there is intubation and drainage of the stomach, we cannot tell in a particular instance whether a stimulus which augments the secretion is in fact pancreatic stimulus, or acts primarily on the stomach, and increases pancreatic secretion because of increased gastric secretion. In the latter case the pancreas is stimulated secondarily by the acid of the gastric juice.

I think that that difficulty of interpretation is applicable to many of the observations made in this study, and particularly those in which there was an attempt to demonstrate psychic stimulation of the secretion. It is quite obvious that what may have happened is that the patient's gastric secretion was increased and due to the hydrochloric acid entering the duodenum the pancreatic flow was augmented.

The depressant effect of atropine was obtained at the time of minimum secretion. That would mean that its influence was exerted mainly on the basal or fasting secretion. That secretion is known to be largely dependent upon impulses coming over the vagus nerves. Consequently, it is not surprising that atropine should have diminished the flow.

That is quite a different matter from the possibility of using atropine to control pancreatic hypersecretion such as occurs in many fistulous cases. In these instances the secretion is likely to be humoral because it is secondary, usually, to gastric hypersecretion, and in spite of the fact that Dr. Crider and I did report a decrease in response to secretin on administration of atropine; that was with the administration of enormous doses, doses impossible to use in the human.

I think the rule still holds that atropine is not an adequate drug for the control of pancreatic hypersecretion.

DR. BORIS P. BABKIN (Montreal, Canada). A very few remarks may be added to what Professor J. E. Thomas said. You discuss in your paper the diurnal and the nocturnal pancreatic secretion. Since the passage of the gastric juice into the duodenum was not prevented in your patient, it is impossible to speak about the "basal secretion" of the pancreatic juice. As far as I know, cancer of the pancreas does not influence the secretory activity of the gastric glands. Therefore, like in normal persons, acid gastric juice was continuously secreted by a fasting stomach, it passed into the duodenum and stimulated the pancreatic secretion.

In the experiments, in which you studied the influence of diet on the secretory function of the pancreatic gland, it would be very desirable to check the secretory activity of the stomach, since the pancreatic secretion depends so much on gastric secretion.

There is another way to find out the effect of different food stuffs on the secretory function of the pancreas. It is a direct or indirect determination of the pancreatic enzymes. In the latter case the total nitrogen of the juice or its specific gravity will give an indication about the total enzymatic power of the secretion.

What you call the "psychic phase" of pancreatic secretion is presumably the "psychic phase" of gastric secretion. The "psychic" or nervous phase of the pancreatic secretion is extremely insignificant.

I am somewhat doubtful about a direct effect on pancreatic secretion of atropine, which you used in your experiments. Atropine inhibits the gastric secretion, but its effect on the secretory function of pancreas is not clear.

DR. E. NEWMAN (Chicago, Ill.): I agree with Dr. Thomas and Dr. Babkin that some of the effects noted may have been secondary to gastric secretion. However, in this study we were attempting to show what effect the various factors studied had on pancreatic flow. The *mechanism* of these effects would, of course, require a different type of study.

I also agree that atropine is probably not very useful in controlling hypersecretion of pancreatic juice in patients with pancreatic fistula. I have not advocated its use for that purpose. It was used only to demonstrate quantitatively the magnitude of its effect in such a case.

THE EFFECT OF VAGOTOMY ON THE HUMAN COLON*†

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Vagotomy was first introduced as a therapeutic procedure for ulcerative colitis by Dennis and Eddy in 1947. Of their four cases subjected to complete vagotomy, clinical improvement was noted in all during a follow-up period of three months. Subsequently, Dennis has reported results of this operation performed on 25 patients, 14 of whom showed evidence of significant improvement¹.

The anatomical basis for this procedure is not clear; it is not certain that fibers of the vagus nerve actually reach the right colon. In humans the data have been summarized by Kuntz² and in experimental animals by Alvarez³ who quotes reports stating that the gastrocolic reflex in dogs was not affected by bilateral vagotomy.

An unusual opportunity to study the function of the human colon before and after vagotomy has been afforded in the person of a fistulous subject with a large area of evaginated colonic mucosa. He was observed before and after bilateral supra-diaphragmatic vagotomy, performed as a therapeutic procedure for ulcerative colitis.

This subject was a 26 year old automobile mechanic of German-American background, a rigid, dependent, insecure, obsessive-compulsive man who had extreme difficulty in expressing anger or hostility. He had had ulcerative colitis for six years (Fig. 1). Therapeutic cecostomy had been performed 2 years after the onset but because of extension of the colitis an ileostomy was required two years later. Such a segregation of a segment of intestine is often referred to as "putting the bowel at rest". Following this procedure the cecostomy closed spontaneously but shortly thereafter a cecal fistula developed through which a loop of ascending colon and cecum prolapsed onto the surface of the abdomen. A small section of ileum was also included in this isolated loop of exposed bowel.

METHOD

The *motor activity* of the colon was observed and photographed by still and motion pictures. Furthermore pressure changes in an inlying, inflated balloon were recorded on a kymograph. Simultaneous recordings were made from areas in both the ascending colon and the descending or sigmoid colon by introduc-

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† Read at the Annual Meeting of the American Gastroenterological Association, Atlantic City, June 9, 1949.

ing balloons both through the cecostomy opening and a protoscope inserted through the anus.

Blood Flow: Throughout the experimental period, the mucous membrane was kept continuously under observation. Special note was made of changes in color, which varied from a pale yellow-red to a brilliant cardinal. Color read-



FIG. 1. Photograph showing prolapsed segment of cecum and ascending colon. The ileostomy opening is beneath the bag in the subject's left hand.

ings were recorded by comparing the color of the mucosa to an appropriately graded color scale standardized according to the method of Munsell⁴. That color changes predictably reflect changes in blood flow has been demonstrated by Richards, Wolf and Wolff⁵. In general, the redder the membrane, the greater the blood flow.

Lysozyme: Lysozyme concentration in the mucus secretion removed directly

from the surface of the prolapsed mucosa was measured by the viscosimetric method of Meyer⁶.

Mucus Secretion: Mucus secretion was observed to be present on the surface of the colon at all times. When it was scant in amount, it was designated as one plus (1+). When the secretion was so abundant as to actually drip from the surface of the bowel, it was designated as four plus (4+). Two and three plus (2+) (3+) were applied to conditions between these extremes.

pH: The pH of the secretion of the colonic mucosa was estimated roughly by indicator paper. Since by this technic no changes in pH were observed over months of observation and in numerous experiments, the data are not detailed in this report.

Fragility: Fragility of the mucosa was estimated by applying a measured amount of negative pressure through a soft rubber catheter to the surface of the colon. The end point consisted of the appearance of a small, sharply circumscribed area resembling a submucosal hemorrhage. At the start a negative pressure of 100 mm. was applied for sixty seconds. When this was insufficient to produce a lesion, either the pressure or the duration of application was increased in successive steps until a lesion was produced.

In this manner the subject was studied intensively for four weeks before vagotomy and at intervals during the second to the eighth week postoperatively. He was customarily observed at the bedside or in the laboratory one and one-half to two hours after the last meal. On each occasion, control observations of motility, color, and secretion were made while he was resting comfortably and lightly diverted. Specimens of surface secretion were removed for lysozyme determination, the latex balloon inserted and the fragility tested. The location of the balloon was checked by fluoroscopy. Observations were repeated at frequent and appropriate intervals throughout each experiment. Following the control period, a short interview was conducted in order to ascertain the predominant mood and feeling state and to determine what events of significance had taken place in the patient's life since the last observation.

SETTING OF THE OPERATION

When the subject became aware that his physicians were considering subjecting him to vagotomy he became enthusiastic about the possibility. He had read an article in a popular magazine describing the use of the procedure for peptic ulcer. By the time the decision was made to operate, however, he had become impatient and uneasy about the outcome. He was aware that correspondence had been engaged in with another surgeon who had had experience with vagotomy in subjects with ileostomy. When the operation was finally undertaken, he had the mistaken impression that it was being done prior to receipt of the letter from the other surgeon. His anxiety was accentuated by the fact

that his hated sister-in-law had selected this opportunity to move back into his house with her husband. Anxiety mounted, and he resentfully ruminated the thought that he was being "used as a 'guinea pig'." He began to feel that if he had never volunteered for the experiments in the first place, his colon would have been resected by now and he could have been home to deal with her. His resentment and anger were further increased by the behavior of his younger brother. This 17 year old boy had fallen into "bad company", was becoming a "drinker" and spent most of his time "hanging around" on street corners and refused to get a job. The patient resented the fact that the sister-in-law and his father did not try to "manage" the boy and had been totally indifferent to his behavior. The subject believed that if he had been home he could have prevailed upon him to give up his bad habits and find employment. In this setting, the subject developed a severe head "cold" which occasioned a further delay in his operation of two weeks. By this time, he noted for the first time in many months a slight rectal discharge of mucus and pus.

POSTOPERATIVE COURSE

Following vagotomy, he recovered from the anesthetic promptly, but was intensely resentful to learn that the chief surgeon who had originally suggested the procedure had not been the one that performed it. He then became more and more anxious and resentful, believing that he had been further "experimented" upon. He felt helpless in his present position to deal with the situation concerning his sister-in-law. He became grim and taciturn, refusing to divulge the reasons for his concern until two weeks later. Within two days after the operation, the exposed area of colon had contracted from its former size of 7" by 2 $\frac{3}{4}$ " to 3 $\frac{1}{4}$ " by 2 $\frac{1}{4}$ ". There were no visible peristaltic waves, and the membrane was engorged and scarlet red (90). Its surface was dotted with numerous petechiae and small fresh ulcerations. It was fragile to the point where bleeding resulted from gentle swabbing with cotton. A profuse grey-white, thick, foul-smelling discharge exuded from the stoma. Cramping lower abdominal pains were severe. This condition persisted and for two weeks postoperatively he had a sustained fever with rectal temperature from 100°F to 102°F.

For the first 4 days postoperatively the stomach was drained continuously and the patient was administered fluids intravenously. Following removal of the stomach tube at the end of this time, the patient noted difficulty in swallowing, epigastric fullness with pain, distension and nausea. Vomiting was frequent and at times occurred after every attempt at food taking. Drainage from the ileostomy was so profuse that the bag required emptying every two to three hours in contrast to the usual twice daily. It was of special interest that the intensity of the nausea, epigastric fullness and vomiting varied considerably from day to day. On days of relatively good spirits, feelings of security and

calm, he was able to eat and retain three small meals without undue discomfort. On days of anger, resentment and hostility, his dysphagia was very severe and he vomited after each effort at food taking, as well as during the night. For example, on a day following a visit from his relatives during which the younger brother's behavior and the sister-in-law's attitudes were discussed, he had extreme difficulty in swallowing his food, had retrosternal pain on swallowing, felt "full" after one or two bites of food and vomited three times during the night. One evening he was informed by his relatives that the city planned to evict them from their home in order to expand a nearby airport. The following day he was able to eat only a few mouthfuls of food, complained of abdominal distension and fullness and vomited three times.

The rectal discharge of muco-pus subsided at the end of 2 weeks. He had finally utilized his opportunity to express freely his hostile and resentful feelings. Suggestions were made for improving his home situation, and he was given a great deal of reassurance and encouragement. Within 48 hours of this free unburdening of his conflicts, the colon elongated to its former size of 7 by $2\frac{3}{4}$ inches, the color faded to 50 and the purulent discharge from the stoma and rectum ceased. Petechiae disappeared and now fairly vigorous swabbing of the mucosa with cotton failed to cause bleeding.

TEST FOR COMPLETENESS OF VAGOTOMY

Prior to operation intravenous injection of 20 units of regular insulin was followed by a brisk increase in gastric acidity. Thirty days postoperatively the test was repeated, but no increase in gastric acidity followed the injection of insulin. As interpreted by Hollander⁷ and others, this is evidence of complete section of vagus fibers at operation. The response before operation is shown graphically in Fig. 2.

Effects of Prostigmine: The effects preoperatively of this potentiator of acetyl choline are to be discussed in detail elsewhere⁸. The experiment was repeated on a day of relatively good spirits and relaxation during the third post operative week. 0.0002 gm. were injected subcutaneously. The result was closely similar to that prior to operation. Within ten minutes, there followed an increase in blood flow manifested by a rise in the color scale readings from 40 to 60 and enhancement of the contractile state and motor activity of the colon. The effect persisted for 30 minutes and then the color and contractile activity resumed their former state.

COMMENT

The effect or lack of effect of prostigmine on the colon is not a reliable criterion of the presence or absence of cholinergic fibers. Although prostigmine's

chief action is to potentiate the effect of acetyl choline released at the nerve terminals by inhibiting cholinesterase, it has been shown to exert a weak acetyl choline-like effect of its own^{9, 10, 11}.

REACTIVITY DURING DISCUSSION OF CONFLICTS

A previous communication has described the experimental production of colonic hyperfunction by a discussion of relevant personal conflicts^{12, 13}.

In brief, this type of experiment consisted of measuring colonic function

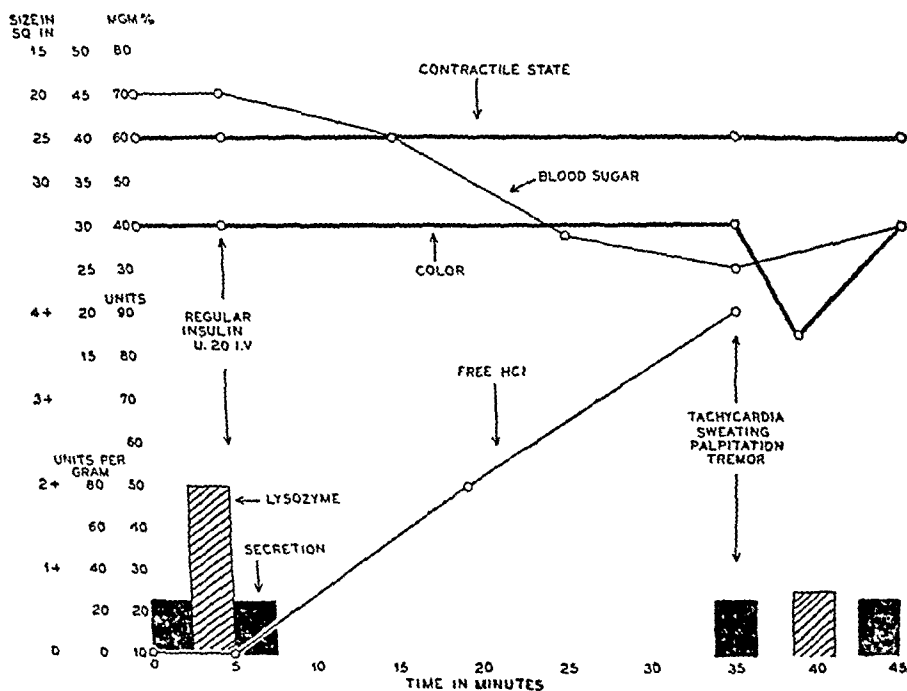


FIG. 2. The effect prior to vagotomy of intravenously administered insulin (20) on the blood sugar, gastric free hydrochloric and colonic function. Secretion, contractile state, color and lysozyme refer to colonic function. Contractile state is expressed in square inches of exposed colonic mucosa. The color of the colon is represented by units of a standardized color scale. Mucus secretion is represented in terms of one to four plus and lysozyme is calculated in units per cc. of mucus secretion removed directly from the surface of the colon.

as above, before, during and after a discussion of topics of personal concern to the patient which were associated with conflict and resentment. An example of such an experiment done during the preoperative state is shown graphically in Figures 3 and 4. Control observations showed a relatively hyperactive bowel. The membrane was moderately engorged and red (60). The subject had been humiliated over the way he had been treated in the hospital and he felt angry

INTERVIEW - PRE VAGOTOMY

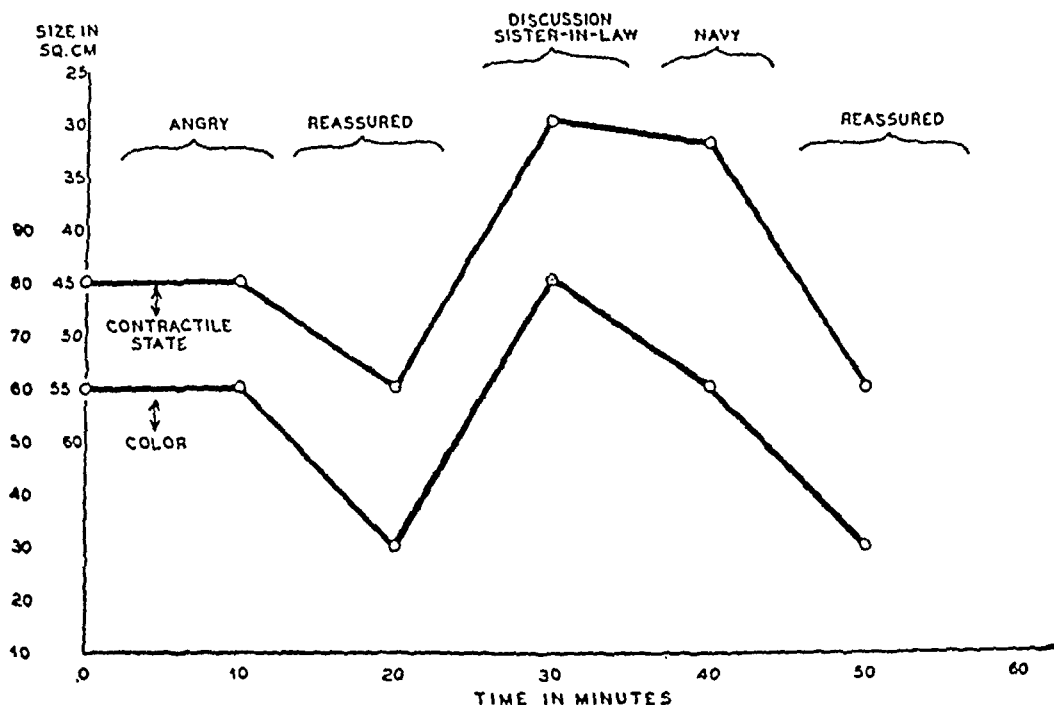


FIG. 3. Graphic representation of the alterations in contractility and blood flow in the exposed prolapsed colon during discussion of personal problems during the preoperative period. Contractile state expressed in terms of square centimeters (length times width) of colon exposed. Blood flow is plotted in numerals corresponding to the graded colors of the color scale. Note the diminution of blood flow and contractility increase during phases of calm and security induced by reassurance. Blood flow and contractility increase during feeling states of anger and resentment experienced by the subject while discussing his sister-in-law and his treatment while in the navy.

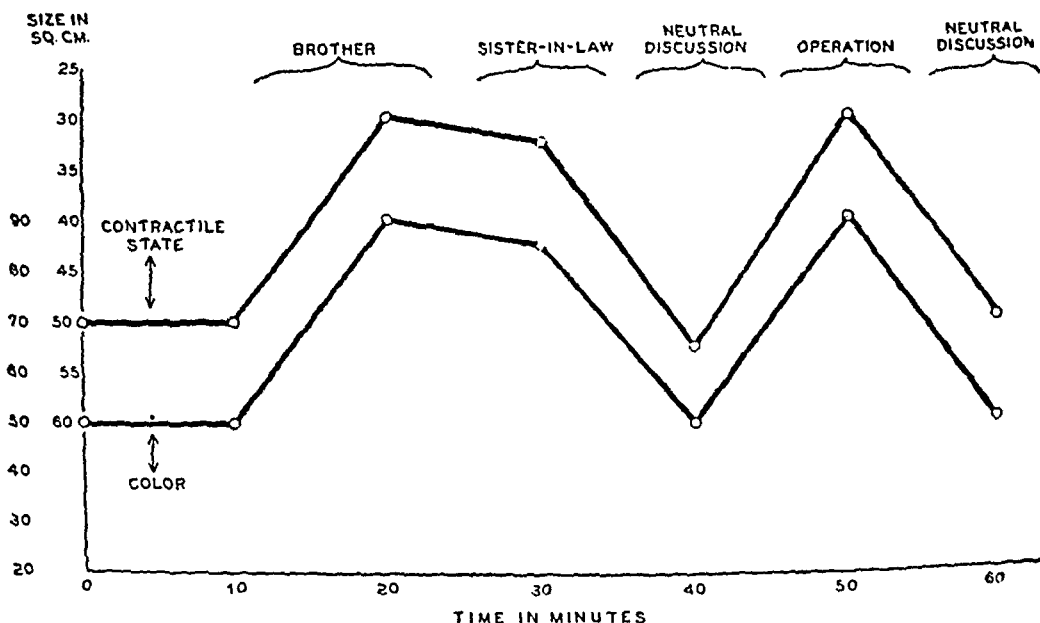


FIG. 4. Alterations in contractility and blood flow in the exposed colon during discussion of sensitive personal problems during the post-operative period. Compare with Fig. 3. Note the increase in blood flow and contractility during anger and resentment experienced by the patient during a discussion of his brother and his sister-in-law, and his operation. Note the fall in blood flow and diminished contractility during calm and security induced by reassurance.

and resentful. He was allowed to ventilate his hostile feelings and in twenty minutes felt calm and relaxed, the bowel was less active, the color had fallen to 30, and the bowel became less contracted. The topic of his attitude toward his sister-in-law was abruptly introduced into the conversation. Within a few seconds the bowel became redder (70), and more contracted. This situation persisted for 3 minutes when the conversation was abruptly changed to neutral and diverting topics. Thereupon the colon blanched to a color of 30 and became less contracted. These effects were repeatedly observed during experimental interviews.

Following the vagotomy such effects were still readily demonstrable. There was no significant difference in the behavior of the colon during discussion of personal conflicts.

For example, on one occasion when the colon was of average color (50) and the size of the exposed mucosa was $6\frac{1}{2}$ by $2\frac{1}{4}$ inches, a discussion of the behavior of the subject's brother was undertaken. He reacted with anger saying "I'll never do anything for him again," the colonic mucosa became engorged and blushed to 90 and the exposed loop of bowel contracted to $5\frac{3}{4}$ by 2 inches. Similar reactions of anger accompanied discussion of his sister-in-law and the operation (vagotomy) and were also associated with increased blood flow and contraction of the bowel. During reassurance and diversion, however, the subject relaxed and the colonic hyperfunction subsided.

EFFECT ON THE GASTROCOLIC REFLEX

Detailed observations on the function and behavior of the colon following the ingestion of a meal are reported elsewhere^{12, 13}. Of eight observations the following changes are typical of those recorded during relative calm and security.

Within 3 to 5 minutes after finishing the meal, a slight reddening was noted (an increase of 5 to 10 units on the color scale), accompanied by an increase in motor activity and a diminution in the size of the exposed loop by about 10 per cent. At 15 minutes, the rise in color amounted to 15 to 20 units, vigorous and frequent contractions began to appear and secretion increased from one plus to two plus. The maximum changes were noted at 30-35 minutes, when the color reached 90, four plus secretion and almost continuous contractions were noted. Following this apex of activity, there was a gradual diminution in blood flow and motor activity so that at the end of 90 minutes control levels were reached. Lysozyme concentration in the colonic secretion increased during the gastrocolic reflex (Fig. 5).

During the postoperative weeks these observations were repeated. Following the ingestion of a meal there was again noted a brisk increase in motor activity, blood flow and secretion in the colon (Fig. 6).

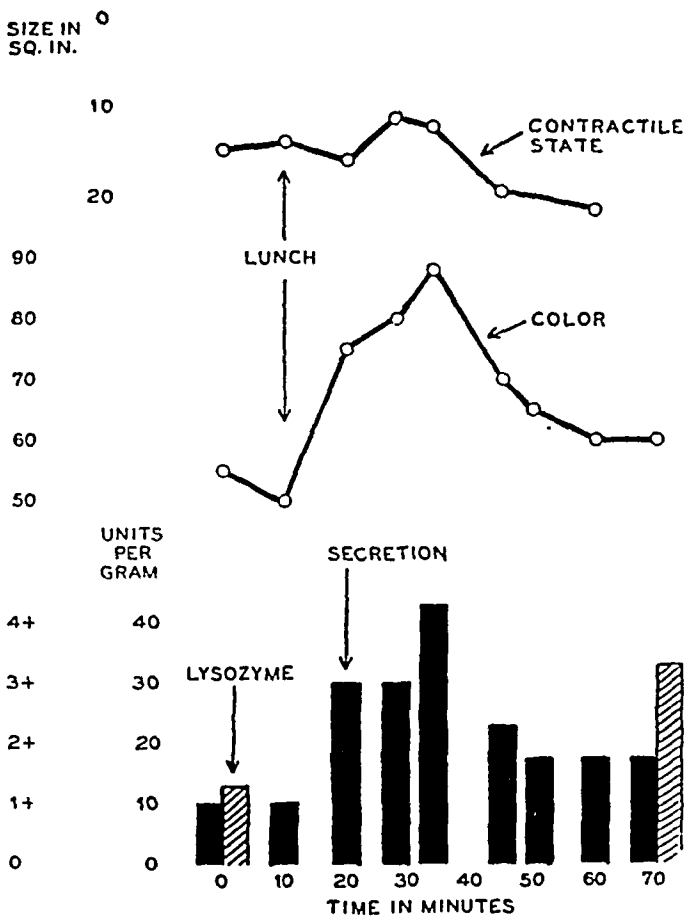


FIG. 5. Graphic representation of the gastro colic reflex prior to vagotomy. Contractile state as in Figure 3. Mucus secretion expressed in terms of one to four plus. Lysozyme in units per cc of secretion removed directly from the surface of the colon.



FIG. 6. The gastrocolic reflex during the postoperative vagotomy period. Values plotted as in Fig. 5. Note the prompt rise in contractility, blood flow and secretion following the meal, as was observed in the pre-operative period.

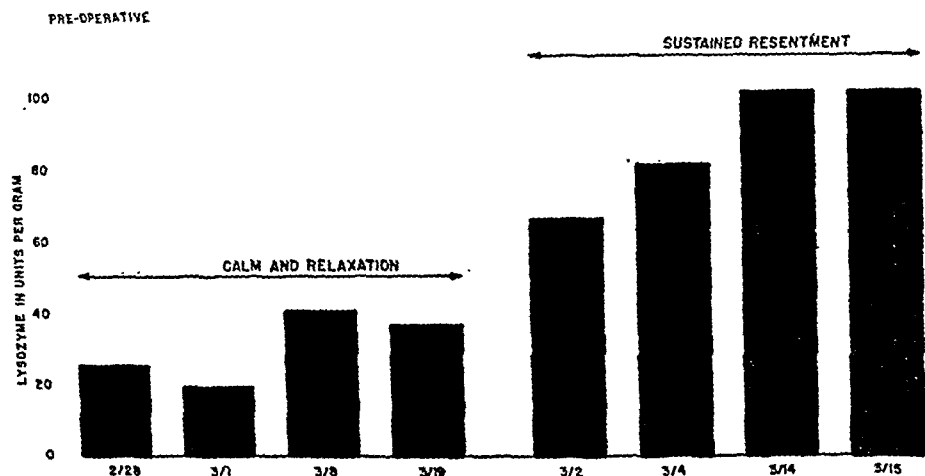


FIG. 7. Pre-operative observations. Lysozyme concentration in the secretion removed from the surface of the colon. Note the relatively low concentrations of lysozyme during days of calm, security and relaxation. On days marked by anger, resentment or hostility, the lysozyme concentration is higher.

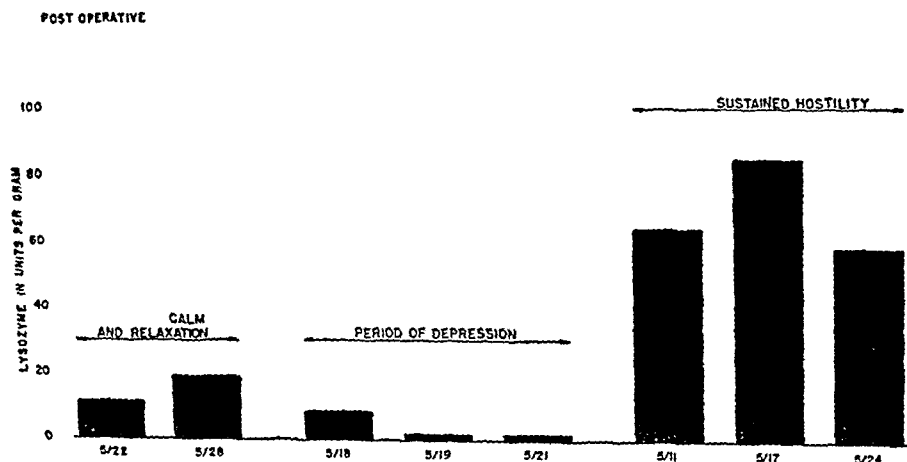


FIG. 8. Lysozyme concentration in the secretion removed from the exposed mucosa following vagotomy. Compare with Fig. 7. Note similar fluctuation in concentration with varying mood as in the pre-operative period. The low values observed during depression are discussed in another publication (11).

EFFECT ON LYSOZYME SECRETION

Variations in the concentration of lysozyme in the secretion removed directly from the surface of the colon prior to vagotomy are described in a previous report¹⁴.

Values as high as 100 units per cc. were noted on days of anger, hostility and resentment (Fig. 7). On days of relative calm, security and relaxation, however, the values were low varying from 19 to 40 units per cc.

Similar variations in lysozyme concentration were observed during the post-vagotomy period. On days of anger, resentment and hostility, lysozyme concentrations of 62, 62.5 and 83 units per cc. were found, while on days of relative calm, security, relaxation and good spirits, values of 11.4, 10.3 and 19 units per cc. were obtained. (Fig. 8).

General Comment: These studies indicate that vagotomy in this subject did not alter the function of the human colon. The response of the bowel to the pharmacologic agents, its reaction during emotions and feeling states, the gastrocolic reflex and the secretion of lysozyme were all essentially the same in the pre- and postoperative states. These data suggest but do not prove that the vagus nerve in this human subject does not innervate the cecum and ascending colon. In any case, regardless of innervation, it is clear that the reactivity of his colon and its capacity to develop an acute exacerbation of ulcerative colitis were not impaired by bilateral vagus section.

SUMMARY AND CONCLUSIONS

From a direct study of the colonic mucous membrane and measurements of contractile activity, mucus and lysozyme secretion in a single subject with ulcerative colitis before and after vagotomy, there was no evidence that vagotomy altered the behavior of the colon or protected it from acute exacerbations of chronic ulcerative colitis.

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STUDIES IN ULCERATIVE COLITIS

I. A STUDY OF THE PERSONALITY IN RELATION TO ULCERATIVE COLITIS*

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In the field of gastroenterology, there can be no doubt that some syndromes are psychosomatic in nature and belong almost entirely in the realm of psychiatry. These conditions are accompanied by at most physiological disturbances and are characterized by the absence of any demonstrable structural change. On the other hand, in certain pathologic conditions such as peptic ulcer and ulcerative colitis, the role of the psyche is not clearly delineated. Psychological attitudes unquestionably modify the course of many physical diseases including peptic ulcer and ulcerative colitis. However, the role of emotional factors in the pathogenesis of these diseases has not been clearly established. It would appear to remain uncertain as to what role psychological factors play in the longitudinal course of the life history of ulcerative colitis. It is with the hope of obtaining more definitive data on these aspects of the problem that a long range study of ulcerative colitis has been undertaken at the Graduate Hospital of the University of Pennsylvania.

A complete study has been carried out on each patient. Repeated observations of the status of the disease have been made by means of correlation of clinical, sigmoidoscopic, roentgen and laboratory findings. During the course of psychiatric study, to be described, a baseline of the personality pattern has been obtained primarily. In addition, attention has been given to the significance of various emotional incidents in relationship to onset and course of the disease. The first part of the study to be reported here deals with the personality make-up of patients with ulcerative colitis.

It has been generally assumed that certain so-called psychosomatic diseases are associated with a more or less definite personality makeup¹. There are those who have suggested that the personality traits are so definitive that they are almost an inseparable part of certain diseases^{2, 3, 4, 5, 6, 7, 8}. In reviewing the literature, one is impressed by the emphasis placed upon the association of the so-called oral type of personality with peptic ulcer, and the anal type of personality with colitis⁹. It is gratifying to note that the trend has changed somewhat and recent workers such as Alexander have found that definite personality types cannot be closely correlated with distinct entities¹⁰. However,

* Read at the Annual Meeting of the American Gastroenterological Association, Atlantic City, June 9, 1949.

every mature clinician does know or can at least sense that there are fairly constant and moderately numerous traits of personality which are common to a good many so-called psychosomatic diseases, including ulcerative colitis¹¹. We hope that this study may help to clarify the moot question as to the consistent presence in patients with ulcerative colitis of specific personality traits.

In the hope that clinical descriptive personality studies might obtain a greater degree of objectivity, a Rorschach test was done on every patient except one. In addition, an attempt was made to correlate the personality studies with an evaluation of the factors in the early development of the patient tending to create the existing emotional reactions.

It is evident that there are no standards which can be utilized in describing personality as a whole. It becomes necessary, therefore, to describe specific traits and to determine their relative incidence in ulcerative colitis. In the future these will be compared with those of normal persons and with those found in other diseases such as peptic ulcer. We feel that this method, although crude, is, in a measure, factual, particularly if great care is used in defining the terms to be used. For this reason, definitions for all traits are included. It will be noted that there is considerable repetition and overlapping in the definition of the various terms used. This is unavoidable for two reasons: (1), because a great many of the attitudes described are the result of those inborn, unlearned, ever present tendencies known as instincts, and (2), because most emotional expressions are as yet not subject to clear verbal description.

ANALYSIS OF MATERIAL

This report is based upon a study of twenty patients followed in the Departments of Gastroenterology and Psychiatry at the Graduate Hospital of the University of Pennsylvania since 1939. All patients were examples of chronic ulcerative colitis of the ordinary type in which at least the rectum, sigmoid and descending colon were involved. Instances of right-sided colitis, colitis with skip areas, as well as ileocolitis were omitted. A history of amebic or of bacillary dysentery was not obtained. Repeated examinations of the stools failed to reveal either trophozoites or cysts of ameba. Agglutination tests for the dysentery organisms were negative. No specific etiologic factor, either bacterial or viral, could be detected in any of these patients. The sigmoidoscopic and roentgen findings were characteristic of chronic, non-specific, so-called idiopathic ulcerative colitis in every instance.

The age of these patients at the time of onset of the disease varied from fourteen to forty-five years, and the distribution is given in Table I. The average age of patients at the time of onset of the disease was 22.7 years. There were twelve males and eight females in the series.

The clinical and pathological features of the disease in the twenty patients included in the study may be summarized as follows. In thirteen instances, the clinical course of the disease was characterized by asymptomatic periods of remissions, alternating with relapses. There were five examples of chronic continuous ulcerative colitis without remissions. In the remaining two patients the disease began as an acute severe fulminating process. In one of these a remission was achieved and the subsequent course of the disease was characteristically that of the chronic relapsing variety. In the other patient with the acute fulminating type of onset, the clinical course subsequently was that of chronic continuous ulcerative colitis.

The majority of the patients had extensive involvement. In eleven instances the entire colon was involved. In five the distal two-thirds of the colon participated in the inflammatory process, and in the remaining four, the entire left colon was diseased. The pathologic status, insofar as that could be obtained by sigmoidoscopic and roentgenologic study, likewise indicated extensive involvement. The disease was classified as being far advanced in ten instances,

TABLE I

AGE—DECADE	NUMBER OF PATIENTS
0-10	0
10-20	7
20-30	8
30-40	3
40-50	2

moderately advanced in seven, and in the remaining three the disease was characterized by a diffuse granular change as shown by sigmoidoscopy and x-ray without evidence of fibrosis or polypoid change.

A striking feature of these cases was the high incidence of polypoid change. Polypoid hyperplasia, often to a very marked degree, was present in twelve patients. Polyarthritic symptoms occurred in one person. One patient was subjected to ileostomy. Two other patients required colectomy.

It may be seen from this brief review that the patients selected are all bonafide instances of moderately severe or extremely advanced ulcerative colitis, and that each of them can be classified as belonging to the ordinary type of non-specific or idiopathic ulcerative colitis in which continuous involvement of the colon extended for varying distances above the rectum, which was always involved, into the higher levels of the colon.

PSYCHOLOGICAL STUDY

The personality study was carried out by two methods: a.) psychiatric interviews of the patient and if possible members of the family; b.) the

Rorschach test. The results of these studies will be discussed under three headings: a.) personality studies by means of psychiatric interviews; b.) personality studies by means of the Rorschach test; and c.) factors in the early development which may explain the personality traits of patients with ulcerative colitis.

A. Personality Studies by Means of Psychiatric Interviews

The psychiatric interviews were really therapeutic sessions with an attempt to develop a relationship between the therapist and the patient, and the utilization of that relationship in enabling the patient to overcome his personality difficulties.

The interviews with each patient varied in number from fourteen to one hundred and twenty. Most patients were seen daily while in the Hospital and then followed weekly. The period of observation differed from patient to patient, the average time being two years.

Like other psychological procedures, these studies depend a great deal upon the training and ability of the investigator, and more particularly on his ability to remain objective, insofar as it is possible in psychological investigations. With this in mind, an attempt was made to break down the personality traits into components capable of definition. The findings were recorded in these cases with the hope of eventually picking out some factors that are specifically significant in ulcerative colitis for future comparison with studies in other diseases. It is, therefore, our purpose to define each of these factors and record their frequency in the twenty reported cases.

The personality traits are discussed under fifteen headings. It should be stressed that some of these characteristics differed from patient to patient, and more particularly varied in degree in the same patient from time to time, often in relationship to the physiological disturbances in the colon. However, in this study, the general outline of the personality is considered and the variations in the relation to the progress of the disease shall be reported in a subsequent presentation.

In describing the traits it was deemed advisable to present them in the order of their development from a psychopathological standpoint, rather than from the order of their relative clinical importance.

I. *Tension*. The term tension as used by physiologists is described as a state of stretch produced by a stimulus. From the psychiatric standpoint, tension is described as a physiopsychological reaction characterized by an intense state of feeling or effort, either pleasant or unpleasant, with or without a known cause, resulting in excessive stimulation of the musculoskeletal,

sensory, and visceral systems with resultant increased activity and heightened expectancy of the organism. It may be relieved in the following ways:

- a. by a decrease of the stimulus.
- b. by a withdrawal of the organism from the stimulus.
- c. by direct activity in answer to the demands of the stimulus.
- d. by converting the total energy produced into a somatic reaction affecting either a body system or a specified anatomical area, i.e. organ dysfunction or hysterical paralysis.

Tension was present in each of the twenty patients.

II. *Anxiety*. This is a form of affectivity recognized introspectively as an unpleasant affect accompanied by fear without any known cause or with the cause inadequately understood or mistaken and manifested objectively by change in the neuromuscular, autonomic, visceral and sensory functions.

Anxiety was present in nineteen of twenty patients.

III. *Agression*. This signifies action carried out in a forceful way. Aggressive impulses are biologically determined and when sublimated serve to foster progressive and constructive forms of adaptation. Frequently aggression is accompanied by hostile trends directed either to an object in the outside world or to self and conducive to both states of tension and anxiety.

Agression was present in twelve patients.

IV. *Passivity*. Passivity is an attitude in which the individual appears to be abnormally receptive and enduring without overt-resistance, resentment or emotional disturbance. This surface passivity often harbors hostility which may lead to anxiety and tension.

Passivity was found in sixteen of the twenty patients.

V. *Inability to assert self*. Inability to assert self may be defined as an attitude whereby the individual is unable in his relationship with other people to express his wishes or ask for something in his own interest, to state an opinion, or express criticism, and to select his associates according to his ideas.

This was present in each of twenty patients.

It is of great interest to note that though aggression was found in sixteen patients, the inability to assert self was almost a universal finding in this series. This is not hard to understand when one considers the relative frequency of passivity and dependency in this group of patients.

VI. *Dependency*. This is an attitude on the part of the individual to abnormally lean on others for advice and guidance, accompanied by inability to make decisions, and often accompanied by tension and anxiety due to the fear of losing emotional support.

Dependency was found in fifteen of twenty patients.

VII. *Indecision*. Indecision is an attitude interfering with the ability to make final and ultimate decisions. It implies the inability to face an issue and react constructively. It may or may not be associated with dependency.

This was found in eighteen of twenty patients.

VIII. *Perfectionism*. This is an attitude whereby the individual strives to attain completeness in all details in order to avoid tension and anxiety.

This was found in twelve of twenty patients.

IX. *Conscientiousness*. This is a sense of right or wrong, of moral good and blameworthiness of one's conduct or character. In psychopathological states, the average normal conscientiousness is modified by feelings of guilt for failing to achieve certain objectives or exaggerating past attitudes in the light of self-punishment. This abnormal conscientiousness leads to states of tension and anxiety.

This was present in fifteen of twenty patients.

X. *Guilt*. Guilt may be defined as an attitude whereby the individual feels that he has failed to live up to his ideals and constantly has a sense of awareness of having committed an offense.

This was present in eighteen of twenty patients.

XI. *Hostility*. Hostility is an attitude of ill-will, resentment, or desire to thwart which is usually masked by aggression with rationalization, anxiety and tension states.

This was present in nineteen of twenty patients.

XII. *Sensitivity*. Sensitivity may be described as the feeling tone of the individual which accompanies stimulation of the perceptive organs (eye, ear, etc.). In psychopathological states, the feeling tone is out of proportion to the nature or to the degree of the stimulus.

This was present in each of twenty patients.

XIII. *Aestheticism*. Aestheticism is the ability of the individual to appreciate or be sensitive to art or music.

This was present in only six of twenty patients.

XIV. *Rigidity*. Rigidity is an attitude whereby the individuals' emotions or affects remain constant in the face of topics that normally call for a change in emotions or affects.

Rigidity was not present in any patient.

XV. *Immaturity*¹². The immature adult is predominantly dependent and unable to accept responsibility. Because of his need for support and reassurance he is usually attached to either a parent or a parental substitute. He is uncooperative, self-centered and does not evaluate situations realistically, but only in relation to himself. If he is productive, it is in response to obsessive demands as a result of feelings of inferiority and the need to compete excessively with others. His conscience may be so strong as to plague him with guilt

about all his activities, or so weak that he lacks any moral restraining force. It is never in harmony with the rest of his personality.

His sexuality is not free but may be inhibited to such a degree as to prevent normal mating, or existing as an excessive uncontrolled instinctual drive as a result of over-compensation for his own feelings of inadequacy. Hostility is usually excessive and is apt to be directed either at himself or others in response to minimal stimuli. He is not able to utilize it in constructive or recreative activity. He is not flexible or adaptable to changing situations. As a result of these many factors, anxiety becomes manifest. He may have the physical and intellectual capacity to function but because of uncontrolled emotional reactions he is unable to do so.

Immaturity was present in nineteen of twenty patients.

B. Personality Studies by the Rorschach Method

The Rorschach test may be defined as a procedure used to determine the various intellectual and emotional processes occurring in the individual. It is a projective test in that the individual projects or puts out his thoughts concerning the test material without any help being given him. In its application the patient is shown ten¹⁰ cards on each of which is a standard ink blot figure with two symmetrical halves. Five of the ten cards are dark gray but with many different shadings. Two are gray and red. Three are multicolored. In the test procedures the patient is asked to state what he sees in the relatively formless blot, what it looks like, what it makes him think of, or suggests to him.

By creating meaningful forms out of meaningless material he reveals fundamental traits in his own character. In his responses the patient externalizes his conflicts and significant attitudes of his personality. The patients' responses are scored and evaluated by means of an elaborate system in which perception and association of the blots have been correlated logically and empirically. It cannot explain how personality developed but reveals the underlying structure which makes the patients' behavior understandable. This method is by no means infallible but is helpful in determining the qualitative degree of personality disturbance and in doubtful cases, the organic, psychotic, or neurotic elements present. The various factors of the Rorschach tests will now be briefly discussed under two chief headings, the intellectual and the emotional aspects. The terms used in this study will be defined when it is felt they are not self-explanatory.

INTELLECTUAL ASPECTS

1. *Mental Level.* Mental level is the mental capacity as evaluated by a diversified battery of psychometric tests. The Rorschach sometimes reveals potentialities not shown by other tests.

- a. very superior—2 patients.
- b. superior—4 patients.
- c. above average—6 patients.
- d. high average—5 patients.
- e. average—2 patients.

2. *Decreased Performance Due to Conflict*. Sixteen had decreased performances due to conflict. Three did not have decreased performance due to conflict.

3. *Capacity for Creative and Imaginative Thinking*. Only three had capacity for creative and imaginative thinking.

4. *Flexibility of Thinking* is the capacity to change concepts and manner of intellectual approach in order to arrive at deductions.

Only two of nineteen patients were capable of flexibility in their thinking.

5. *Perfectionism*. Only nine of nineteen patients were perfectionists in their behavior.

6. *Ambition*. This is an attitude whereby the individual has an uplifting desire to achieve or attain a goal.

Four of these patients had ambition.

7. *Ambition Within Limits of Capacity*. Two of the patients had ambition within limits of their capacity. In most instances their ambition was far below their limits of capacity.

8. *Compulsive Drive to Achieve Beyond Capacity*. Two patients had a compulsive drive to achieve beyond their capacity. In at least one of these patients (no. 7) this was not seen clinically.

9. *Ability to Think Along Group Lines*. Ability to think along group lines is the ability to think in a conventional pattern. This may include original thinking.

Eighteen of nineteen patients had ability to think along group lines.

EMOTIONAL ASPECTS

1. *Emotionally stimulated by environment*.

- a. Eight patients had extreme emotional responsiveness to environment.
- b. Nine patients had average emotional responsiveness to environment.
- c. One patient had below average responsiveness to environment.
- d. One patient had a psychotic type of responsiveness to environment.

2. *Inability to Establish Stable Relationships*. This may be described as emotional instability, impulsivity and easy change of love object.

Seven of nineteen were unable to establish stable emotional relationships.

3. *Emotionally Responsive but Overly Controlled*. This is the ability to respond to others with warmth, stability and depth of feeling, but wary of involvement and loathe to express feeling.

Two patients were overly controlled in their emotional responsiveness.

4. *Depression.* This is a withdrawn state in which the individual although he may be stimulated by emotional contacts with others, has been so traumatized that he emphasizes the gloomier aspects of life and cannot express himself in a warm or spontaneous manner (it usually is accompanied by other indications of anxiety and loss of self-esteem).

Five of the patients revealed considerable depression.

5. *Excessive Fantasy Living.* This may be described as day dreaming in contradiction to what is logical and realistic; is composed of images or representations existing in or elaborated in the unconscious mental level and as such is free from restraints of reality.

Eleven of the patients made excessive use of phantasy life which they took seriously.

6. *Emotional Immaturity.*

Emotional immaturity was revealed in all of the tests except one, which was that of a sixteen year old girl.

7. *Anxiety.*

Eighteen of the patients had anxiety. The only test that did not show anxiety revealed psychotic material.

8. *Aggression.*

Nine of the nineteen patients had considerable aggression.

9. *Passivity.*

Nine of the nineteen patients had passivity to a marked degree.

10. *Dependency.*

Eleven of the nineteen cases revealed a marked degree of dependency.

11. *Hostility.*

Thirteen of the nineteen patients revealed a marked degree of hostility.

12. *Guilt.*

Seventeen of nineteen patients had an excessive amount of guilt feelings.

13. *Indecision.*

Thirteen of the nineteen patients revealed an excessive amount of indecision in their personality-make-up.

14. *Compulsiveness.*

Seven of the nineteen patients had a large amount of compulsiveness in their make-up.

15. *Problem in Relation to Mother.*

Seventeen of the nineteen patients had problems in relation to their mother.

16. *Problems in Relation to Father.*

Eleven of the nineteen patients had problems in relation to their father.

17. *Problems in Relation to Both Parents.*

Eleven of the nineteen patients had problems in relation to both parents.

18. *Sibling Rivalry.*

Only two of the patients showed evidence of sibling rivalry.

19. *Masculinity or Femininity Not Established.* This may be defined as ambivalence to male and female role. This is usual in an adolescent but in an adult is indicative of latent homosexuality.

In ten of the patients masculinity or femininity was not established.

20. *Good Potentialities for Establishment of Masculinity or Femininity.* This may be defined as satisfactory identification with persons of the same sex on the positive side, and only slight latent identification with the opposite sex.

Six of nineteen patients had a good potentiality for complete establishment of masculinity or femininity.

21. *Complete Male or Female Identification Accompanied by Doubts.* This is a feeling of insecurity about being sufficiently male or sufficiently female.

Four of the patients with complete male or female identification had doubts concerning it.

C. *Factors in the Early Development Which May Explain the Personality Traits of Patients with Ulcerative Colitis*

An attempt was made by psychiatric interviews to ascertain early experiences, fantasies, or relationships which may account for the development of the personalities of the patients under investigation, and perhaps explain the occurrence of ulcerative colitis. Here again there are many difficulties in obtaining satisfactory data, and we are fully aware of the fact that the information may not be fully accurate. In the interest of the greatest possible accuracy, and perhaps as a guide for future studies, the subject was broken down into a number of factors which are considered separately.

1. *Emotional Illness in the Family*

- a. Emotional illness in the mother—10
- b. Emotional illness in the father—7
- c. Emotional illness in one sibling—1
- d. Emotional illness in two or more siblings—2
- e. Psychoses—2
- f. Mental deficiency—1
- g. No emotional illness was found in the family of six of the patients.

Fourteen patients had twenty-six known relatives with problems.

2. *Early Relationships to Mother*

- a. Ten of the patients were openly rejected by the mother.
- b. Three of the patients had mothers who were indifferent.
- c. Three of the patients' mothers were domineering.
- d. In four instances the mother was unable to protect the patient from a strict father.

It is worthwhile to note that there was some difficulty present in each patient.

3. *Early Relationship to Father*

- a. Eleven of the patients had excessively strict fathers.
- b. Five of the patients were rejected by the fathers.
- c. Three of the patients' fathers were mild but indifferent.
- d. One father was completely indifferent.

There was some difficulty present in each patient.

4. *Early Relationship to Siblings*

- a. Four of the patients were only children.
- b. Two of the patients were the older of two children.
- c. Two of the patients were the younger of two children.
- d. Five were the youngest in the family.
- e. One patient came from a family of seven.
- f. Eleven had problems in relationship to siblings.

5. *Early Traumatic Gastrointestinal Problems*

Three had early traumatic gastrointestinal problems. They were:

1. Sudden bowel training between twelve and eighteen months.
2. Nausea and vomiting as a child when upset.
3. Gastroenteritis at the age of two.

Six of the patients had physical disabilities in childhood.

7. *Economic Factors*

- a. None of the patients were known to relief agencies.
- b. Sixteen of the patients' families had no financial problems.
- c. Four of the patients' families had some financial stress but all were self-supporting.

8. *Educational Progress at Time of Onset*

- a. Grammar School—two
- b. High School Students—three
- c. High School Graduates—ten
- d. High School, Business or Technical School—four
- e. College Graduates—one

These patients were all in grades commensurate with age and educational opportunities.

9. *Social Adjustment*

- a. Shy and withdrawn—ten
- b. Poor relationships—three
- c. Good relationship—seven

10. *Other Traumatic Experiences in Early Life*

Eighteen had severe early traumatic experiences. They were:

1. Major marital difficulties of parents—three
2. Desertion by father—two
3. Unwanted children—two

4. Rejection by sending away from home—two
5. Raised by grandparents with feeling of rejection by parents—two
6. Death of near relative—two
7. Forced to attend school under unfortunate condition—four
8. Forced to leave school under unfavorable condition—four
9. Expelled from school—one
10. Severe struggle to get education under stress—one
11. Disfiguring eczema—one
12. Obesity—one
13. Rejection by peers—three
14. Sexual traumatic experience—three
15. Forbidden by parents to play with other children—two

DISCUSSION

A. *Personality Traits.* It is evident at a glance that the patients with ulcerative colitis have an abundance of personality traits observed in many people classified as having a neurotic personality. The almost constant occurrence of such traits as anxiety, hostility, tension, indecision, guilt, dependency, passivity, sensitivity and immaturity, and the frequent existence of aggression and perfectionism in the absence of psychotic reactions, justifies the statement that the patient suffering from ulcerative colitis is a neurotic individual.

Our clinical studies would indicate that the majority of these traits existed long before the development of the evidence of ulcerative colitis and that, therefore, these individuals were either overtly or potentially neurotic prior to the development of the ulcerative colitis. It would, therefore, seem reasonable to assume that the physical effects of the ulcerative colitis are not responsible for the neurotic traits, although the disturbance in the colon undoubtedly activated latent neurotic traits and increased existing psychopathological disturbances.

It was gratifying to note that the findings by clinical studies, and the Rorschach test do not reveal any major discrepancies. Since the Rorschach tests are presumably more objective, it is important to observe that on the whole careful clinical studies are conducive to fairly accurate evaluation insofar as psychological studies permit. Neither method reaches the deeper unconscious level of the personality although the Rorschach test may be more informative from this standpoint.

Physicians, who are not preoccupied with the intricacies of psychopathology and psychotherapy may be struck and perhaps be bewildered by the simultaneous occurrence in the same patient of such opposite traits as for instance, passivity and dependency on the one hand, and aggression and hostility on the other. To clarify these apparently contradictory traits would be too lengthy a

task for this presentation. The reader is referred to appropriate works on this subject and especially the works by Horney^{13, 14}. For practical purposes the following may be borne in mind:

a. Most of the so-called "neurotic traits" exist in the normal individual, but in a degree, quality, and combination, which are conducive to good, everyday adjustment. A certain amount of tension, aggression, dependency, and other traits, including anxiety are necessary "seasonings" in everyday activities.

b. In the neurotic, these traits differ from the average normal in the degree, quality and combination, causing pathological reactions. This difference may be crudely compared with formulations in organic chemistry. Thus carbon, oxygen and hydrogen, depending on quantitative differences and combinations, produce vastly different substances.

c. From a psychopathological standpoint, many of the traits reflect conversions, substitutions, compensations and projections. Thus, for example, early guilt feelings are conducive to anxiety, hostility and aggression, or to passivity, dependency and indecision, or to a combination of both.

d. Simultaneous existence of contradictory traits results in a state of emotional disequilibrium, usually at the unconscious level, manifested by physiological and psychological disturbances. Again one may resort to analogy with familiar chemical incompatibilities or to the phenomenon of noise in sound activities.

It is possible that the degree, specific quality, and combination of various neurotic traits may have significance in the problem of ulcerative colitis. Without further study and especially until comparative studies are made with other disease entities, no definite formulation can be deduced from our series of cases. However, based on the study of these patients, the impression emerges that despite their similarity to many individuals suffering from other disease entities, these patients show a patent weakness in meeting everyday problems, and that their inability to assert themselves is greater than in other neurotic people. It should be pointed out here that we do not consider these patients "weak" individuals, although their behavior before treatment usually gives that impression to the casual observer. Most of the patients had strong basic drives, but their inner conflicts prevented them from making constructive use of their strength. None of them could stand up for themselves, yet over half of them showed evidence of unexpressed aggression often to a high degree. In a future paper we shall try to show the relationship of expressed or unexpressed aggression and intestinal symptoms. This point is of value from a therapeutic standpoint.

It is of interest that seventeen of nineteen patients were able to be stimulated by their environment. This fact accompanied by their inability to respond to

stimulation created conflict. Instead of responding they retreated to phantasy living and over half of the patients did this to an excessive degree. From the above discussion it can be readily seen why seventeen out of the nineteen patients lacked ambition. Only three of the patients had capacity for creative and imaginative thinking. This shows the paucity of their inner lives. It is significant that none of these patients had any hobbies or absorbing interests.

One is struck by the total absence of rigidity as a trait in these patients. This may be of considerable prognostic and therapeutic importance. Frank psychotic reactions were conspicuously absent. In one patient, the Rorschach test indicated psychotic trends but clinically there was no evidence of any psychoses.

B. Factors in the Early Development Which May Explain the Personality Traits in Patients with Ulcerative Colitis. A study of the material would again tend to disclose that the early development of individuals who later develop ulcerative colitis is not different from that of other patients with neurotic trends. Indeed, one questions how different is the experience of these individuals from that of the many so-called average normal people who later in life develop no psychosomatic or other psychological difficulties. However, an analysis of some of the details in these cases is of considerable interest.

Emotional Illness in the Family. There was emotional illness in the families of fourteen out of the twenty patients. In ten of these, the emotional illness was in the mother and in seven in the father. It is felt that the early family background from the standpoint of emotional illness may well play at least some role in the development of the personality in these patients. It is to be noted that there was a history of ulcerative colitis in the families of three of the patients.

Early Relationship to Mother. It is held significant that each of the twenty patients had some disturbance in relationship with the mother. Ten of these patients were openly rejected by the mother, and in three, the mother appeared to be indifferent. In another three, the mothers were domineering, and in four, the mother was unable to protect the patient from a strict father.

Early Relationship to Father. Here again one notes definite disturbances. Eleven of the patients had excessively strict fathers; five were rejected by their fathers; and the others had fathers who were largely indifferent to them.

This study would indicate that there is a major abnormal parent-child relationship in the early lives of patients suffering with ulcerative colitis.

Early Relationship to Siblings. The only clearly significant abnormality noted in the early relationships to siblings was a feeling on the part of the patient that they were being discriminated against in regard to the amount of love and affection given them in comparison with other children in the family. It is of interest to note that there were no "oldest" children in the series.

Nine or almost half of the patients were the youngest or only children who are more apt to develop feelings of insecurity or isolation than the oldest who learn to carry more responsibility and possibly develop stronger personalities. The oldest child may get most of the affection which immature parents have to give so that little is left for the youngest. The four "only children" in the series all felt isolated. Only three patients had one other sibling and two of these patients felt inferior to the other child.

Economic Factors. Sixteen of the patients' families had no definite economic problems. It is felt that economic factors in early life probably do not play a major role in the personality make-up of these patients. In this connection, it is of interest to note that Klein¹⁵ states that most of her patients came from the slums. However, our group of patients belonged to the middle and self-supporting working classes.

Educational Factors. These appeared to play no role in this group.

Social Adjustment. The only significant observation was the fact that ten out of the twenty patients were rather shy and withdrawn during their early life.

Physical Disabilities. Only six of the patients had minor physical disabilities in childhood and this cannot be regarded as significant.

Early Traumatic Gastrointestinal Problems. These were meager. Only three patients presented such problems and the latter were not overly impressive.

Other Traumatic Experiences in Early Life. Eighteen of the twenty patients had some form of early traumatic experience. Eleven of these were very serious in nature. Five of the patients had severe sexual conflicts before mid-adolescence and at the time of onset of their illness only six of the twenty patients had potentialities for establishing good heterosexual relationship. Since these experiences varied in kind and severity, it is impossible to draw any definite conclusions as to their value as specific factors in relation to the development of ulcerative colitis. One has the impression that these early experiences may not differ from those in other psychosomatic situations.

In evaluating the factors in the early development, one must bear in mind that this study cannot be considered as complete because of the difficulty of procuring accurate data. It is important to remember that it isn't what occurs in early childhood that is important but it is the value and meaning that the individual gives to these occurrences which later influences the make-up of his personality.

Psychological Determinants for the Development of the Disease in the Colon. It was disappointing to note that there was nothing in these psychological studies to give us any inkling as to why in these individuals the colon was selected as the site of ulceration. Neither the study of the early development nor the personality studies suggested any abnormal preoccupation with the

gastrointestinal tract, any unusual diseases or disabilities pertaining to that tract, or factors of hetero or autosuggestion so commonly observed in other psychosomatic situations, such as cardiac neuroses or traumatic neuroses.

In evaluating the results of the psychological studies in this series, we are keenly aware of the fact that these methods did not permit a satisfactory exploration of the early and deep strata of personality, which would not only explain the various traits, but also possibly the factors determining the localization of the disease process in the colon.

SUMMARY

In the twenty patients of this study, the clinical, laboratory, sigmoidoscopic and roentgen findings were such that each of them could be classified as belonging to the ordinary type of non-specific or idiopathic ulcerative colitis, in which continuous involvement of the colon extended for varying distances above the rectum, which was always involved, into the higher levels of the colon.

These patients were studied from the standpoint of personality make-up by the combined method of psychiatric interviews and the Rorschach test. Each of the various personality traits were defined with the hope of establishing some standard for future study.

Every patient in this group has definite neurotic traits. The following traits were revealed by the psychiatric interview method: tension, inability to assert self, anxiety, and sensitivity were found in all; hostility and immaturity in nineteen; guilt and indecision in eighteen; passivity in sixteen; dependency and conscientiousness in fifteen; aggression and perfectionism in twelve; aestheticism in six, and rigidity in one.

The Rorschach test, which was performed in nineteen out of the twenty patients, revealed the following: inability to respond to stimulation in their environment in nineteen; immaturity and anxiety in eighteen; guilt, lack of flexibility in thinking, and lack of ambition in seventeen; indecision and hostility in thirteen; excessive phantasy life in eleven; aggression and passivity in nine; perfectionism in twelve; psychotic trends in one.

The study of the early developmental factors reveals considerable emotional illness in the family, major disturbances in the parent-child and sibling relationship, and numerous early traumatic experiences not specifically related to the intestinal tract.

CONCLUSIONS

1. Patients suffering with ulcerative colitis are complex neurotics in whose early life there were major parent-child relationship disturbances and other traumatic experiences.

2. These patients present an abundance of neurotic traits commonly ob-

served in the neuroses and other psychosomatic conditions. It is suggested, however, that future studies may reveal that the degree, quality and combination of these neurotic traits may differ materially from those of other so-called psychosomatic disorders. Certainly a study of these traits should prove of value in a more specific understanding of ulcerative colitis.

3. These personality studies do not disclose the reason for the localization of the pathophysiological process in the colon.

4. Obviously none of the personality traits found in ulcerative colitis, when taken alone, are specific for this disease, yet it is felt that the understanding of these traits may be useful in the treatment of these patients.

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THE USE OF DIBENAMINE IN ANXIETY STATES WITH GASTROINTESTINAL MANIFESTATIONS*

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Before our preliminary experience with a new sympatholytic drug, Dibenamine (N,N-dibenzyl-B-chlorethylamine), is discussed, it might be well to review briefly the slow but steady progress in our knowledge of the conduction and transmission of nerve impulses. Since the demonstrations that acetylcholine promotes synaptic transmission of certain nerve impulses and that stimulation of the gastric vagus results in the appearance of acetylcholine in the venous blood from the stomach¹, gastroenterologists have been intrigued with this new field. In 1937 Necheles² presented before this society a theory of the development of peptic ulcer based on the effects of this chemical agent on blood flow through the stomach which is still attractive in view of Alpern's³ recent observations on elevated acetylcholine values in 83 per cent of gastric and duodenal ulcers with a return to normal after gastrectomy or medical treatment.

The role of acetylcholine, cholinesterase and cholinesterase inhibitors in the psychiatric field has recently been reviewed by Wortis⁴. He pointed out that most known convulsants promote acetylcholine production and most anti-convulsants inhibit it. Cocaine, quinine, quinacrine hydrochloride, atropine and hyperventilation (all of which can induce psychiatric disorders) inhibit acetylcholine production whereas electroshock, insulin hypoglycemia and carbon dioxide inhalations (all of which are used in the treatment of psychosis) promote acetylcholine synthesis.

Epinephrine is used infrequently in the therapy of psychosomatic gastrointestinal disorders but the sympathomimetic drugs, amphetamine and d-amphetamine, are being used increasingly in certain emotional states with gastrointestinal components, notably the depressions. Anxiety states occur much oftener in gastroenterologic practice than depressed states—in our experience more than four times as common⁵—and Diethelm and coworkers⁶ showed that anxiety, fear, panic, resentment and anger are accompanied by the presence in the blood of demonstrable adrenergic substances.

Perhaps what is needed more than the therapeutic agents mentioned in the preceding paragraph is an effective adrenergic blocking agent or sympatholytic drug. Such a drug, Dibenamine, is now being studied in several clinics. Related to the nitrogen mustard war gases and possessing a definite antihistaminic

* Read at the meeting of the American Gastroenterological Association in Atlantic City, June 9, 1949.

action, it interests us primarily as a potent adrenergic blocking agent which can be administered by mouth. Rockwell⁷ recently described its use both intravenously and orally in 55 hospitalized psychiatric patients in whom anxiety, fear, panic, resentment or anger were prominent features. He considered the drug's therapeutic effectiveness to range from slight to strong. In his cases nausea and vomiting were the most common toxic effects as related to the gastrointestinal tract.

This report is concerned with our preliminary experience with the oral administration of enteric coated tablets* of Dibenamine hydrochloride (130 mg. each) to 22 ambulatory patients with moderate to severe anxiety states associated with gastrointestinal manifestations. Most of the patients came to the Clinic for thorough diagnostic studies, and the drug was presented to them without comment or suggestion as to its therapeutic or diagnostic possibilities. One tablet was taken with each meal for the first day and two tablets three times a day thereafter for a total of from five to seven days. A few of these patients had organic lesions, such as peptic ulcer or ulcerative colitis, but the majority of cases were diagnosed as cyclic vomiting, pylorospasm, mucous colitis, nervous diarrhea, cancerphobia or other functional disorders.

Seven patients received no significant benefit from the drug; 8 had to discontinue it because of persistent nausea and vomiting with no appreciable beneficial effect and 7 obtained moderate to considerable benefit in both the anxiety state and the accompanying gastrointestinal symptoms. The available evidence seems to indicate that the untoward gastrointestinal reactions are the result of local, not central, effects. No other significant toxic reactions were noted in our cases.

Two cases will be described.

Case 1: J. E., a 56 year old unmarried man, was first treated by us in 1945 for an uncomplicated duodenal ulcer of nearly thirty years' duration. Medical treatment controlled the symptoms for nearly three months after which the patient abandoned his diet, medication and other restrictions with only occasional symptoms until June 1948. He returned to us in November 1948 complaining of continuous abdominal pain radiating to his back; roentgenography revealed an active ulcer on the posterior wall of the duodenum. He seemed extremely agitated but declined to discuss his affairs, insisting that all he wanted to talk about was his stomach. He was given no medication but Dibenamine and no change was made in his diet. The pain disappeared by the fifth day and when we saw him on the seventh day he was relaxed and spontaneously discussed his resentment and anger at his employer who, after twenty years, had become so difficult to satisfy that the patient had decided to seek another job. Symptoms of peptic ulcer did not occur during the next two months, although no follow-up roentgenogram was obtained.

* Kindly supplied through the courtesy of Smith, Kline and French Laboratories, Philadelphia.

Case 2: H. M., a 33 year old divorcee, came to the Clinic with a complaint of severe vomiting spells occurring several times daily for the past eighteen months. Several factors in her history seemed important: she had been indulging in excessive amounts of alcohol, she admitted that she was extremely nervous, and because of persistent nasal blockage she had been using about 6 ounces of 1 per cent solution of neosynephrin hydrochloride as nose drops each week for five years; this was discontinued three days before she came to the Clinic but vomiting persisted. She weighed 162 lb. On admission blood pressure varied from 160 to 185 mm./Hg. systolic and 110 mm./Hg. diastolic. The patient's face was flushed, there was severe, coarse tremor of the extremities, lips and tongue, and the speech was so rapid as to be difficult to understand. Her condition on admission was described by several examiners as a combination of severe anxiety, manic state, hyperthyroid state and early delirium tremens. Except for a high value for the glucose screening test results of laboratory investigations were normal. Basal metabolic rate was -3 . Gastrointestinal roentgenograms were all normal. Vomiting ceased on the third day after the institution of Dibenamine and by the sixth day the patient looked like a different person. She was calm and composed, her blood pressure had dropped gradually to 130 mm./Hg. systolic and 85 mm./Hg. diastolic, her color was normal, and the tremor had practically disappeared. She was able to discuss with us a rather complicated emotional life which largely involved strong resentments toward a "girl friend" with whom she was living.

COMMENT

The therapeutic response in this case was one of the most prompt and dramatic that we have ever seen. Dibenamine was administered only as a therapeutic trial and with great reluctance as everyone who saw her believed she needed immediate institutionalization. The remarkable response was quite unexpected. We are unable to offer more than speculation as to the origins of this patient's illness but it seems reasonable to assume that the adrenergic blocking agent administered to her had some effect on the vicious cycle in which she seemed to be caught. We do not mean to infer that Dibenamine is a cure for all anxiety states but we do think that further studies of the use of it or of related drugs are warranted. It is our belief that as a temporary therapeutic agent it may find a parallel in the use of dextro-amphetamine sulfate (Dexedrine) in the diagnosis and treatment of depressed states.

CONCLUSIONS

Dibenamine was administered orally to 22 ambulatory patients with anxiety states associated with gastrointestinal symptoms. In one-third no effect was noted, in slightly more than one-third the drug had to be discontinued because of persistent nausea and vomiting, and in slightly less than a third definite improvement in the anxiety state and the accompanying gastrointestinal

symptoms was observed. It is realized that this does not represent a controlled study on a statistically significant number of patients, but even from this small experience continued studies of Dibenamine and related compounds would appear to be worth-while. If an active member of this group of preparations can be found which has fewer toxic manifestations, it will undoubtedly have great therapeutic possibilities in the field of gastroenterology.

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DISCUSSION OF PAPERS BY W. J. GRACE ET AL., V. P.
MAHONEY ET AL., AND A. J. SULLIVAN

DR. STEWART WOLF (New York, N. Y.): Although the focus of Dr. Grace's remarks was not concerned with psychosomatic mechanisms as such, the data he presented are sufficiently germane to the later papers that they should be commented upon, especially one point in his methodology. He finds in his subject that exacerbations of colonic disturbances and symptoms corresponded in point of time with conflicts in the life situation.

This is a familiar experience, but the significant point in Dr. Grace's presentation is that by short-term experimental observations he validates the suspicion that the conflict is relevant to the colonic disturbance, by introducing it for discussion and thus inducing a prompt reaction of colonic hyperfunction. The fact that he is able to turn it off again by diversion, reassurance, and the discussion of neutral topics, further substantiates his inference that the personal conflict is related to the colonic disturbance.

Dr. Yaskin's methodology is also of special interest. His paper contains a business-like and quantitative approach to a problem of extremely complex nature, a problem of analyzing personal and personality reactions. I am sure that people could disagree with the traits that he singles out. I am sure they could disagree with his definition of each one, but the important point is that he does define them, and thus he offers us an opportunity to assess the data and evaluate these inferences.

Dr. William Grace and Dr. Thomas Almy, at Cornell, who have also been observing patients with ulcerative colitis from this point of view would, I think, agree essentially that the same outstanding characteristics, non-delineating as they are, are recognizable in ulcerative colitis—the suppressed hostility and the lack of capacity for self-assertion, and I think that it is in this lack of capacity for self-assertion that the individual with ulcerative colitis differs most strikingly from the individual with peptic ulcer, who, as we all know from the positions he occupies in the world around us, has a very highly developed capacity for self-assertion.

DR. T. GRIER MILLER (Philadelphia, Pa.): Dr. Grace's presentation on vagotomy in relation to colon function is significant in that it demonstrates what one would expect in view of the absence of convincing evidence of an anatomical relationship between the vagus and the lower bowel. His studies indicate that vagotomy does not alter the behavior of the colon. Shiffer, of our clinic, also has demonstrated by radiological studies no specific alterations in the pattern or motility of the colon after vagotomy. This leaves unexplained the good results from vagotomy as reported by Dennis and Eddy. One wonders if the improvement in the condition of their patients may not have been due, in part at least, to more rest for the colon, incident to the depressant effect of the operative procedure on the motor function of the stomach and small intestine. Another possibility involves the psychic effect of the meticulous attention given their patients. That, undoubtedly, has been an important factor in the early period of many other forms of therapy that originally were zealously ad-

vocated, but now are discarded. At any rate one must keep an open mind about the subject, and such studies as this one by Dr. Grace and his associates will eventually help to clarify the matter.

Dr. Sullivan's paper arouses interest because again it raises a question as to the specific actions of the parasympathetic and sympathetic nerves in disorders of the gastrointestinal tract. We have been inclined to associate most digestive upsets, both organic and functional, with an overactive vagal influence. On that basis, for instance, vagotomy, as well as the use of the atropine-like drugs, has been advocated.

Now Dr. Sullivan suggests that in certain anxiety states the sympathetic influence may be paramount, even in some patients with peptic ulcer and colitis, and that adrenergic-blocking agents, such as dibenamine, are indicated in them. He implies that these sympathicolytic substances may have their effect on the digestive tract through the local blood flow. The question cannot be answered on the basis of present knowledge. When one thinks of the shunting of blood from the mucosa of the stomach under traumatic conditions, as recently described by Barclay and Bentley, and especially their suggestion that this is under the control of the sympathetics, he realizes how little we know about the circulation through the digestive tract wall, an attractive field now open for intensive and perhaps fundamental research.

DR. SIDNEY A. PORTIS (Chicago, Ill.): You will remember at the last session of the Association I presented two slides showing the innervation of the gastrointestinal tract, especially that of the colon, and said that the vagus innervated the colon up to the ascending limb of the splenic flexure. It took Dr. Connell, a graduate of some 50 years ago, to call my attention to the fact that there was no evidence that the vagus innervated the colon at all.

Subsequent discussions with members of the Department of Anatomy of Northwestern University and the University of Chicago have justified Dr. Connell's statement that as far as they knew, the vagus did not innervate the colon. Dr. Warren McCullough, Neurophysiologist of the Illinois Neuropsychiatric Institute exposed the vagus nerves of a monkey and could not produce peristaltic action in the colon after stimulating these nerves.

Therefore, I now express my humble apologies to the members of the Association for putting this evidence in the literature as to vagal innervation of the colon. I think all anatomists and neurophysiologists agree that the sacropelvic parasympathetic nerves innervate the colon from the ascending limb of the splenic flexure down to and including the anal region.

The psychodynamics and psychogenic factors have been given to us by these discussions. One would get the impression that there are many constellations producing the pathologic physiology which ends up in the disease called ulcerative colitis. I do not think this is true. We are dealing with a disease in which many remissions occur. Relapses can be produced under specific psychological traumatic manifestations. One can directly observe what is going on in the colon at this time as the result of this untoward stimulation.

Of all the diseases of the gastrointestinal tract which yield to a psychosomatic ap-

proach, I am led to believe that one can find a common denominator in ulcerative colitis. It is unfortunate that so many psychiatrists, working on it from different angles, start out with a basic premise and try to prove that this or that emotional conflict will produce the pathologic physiology. All of the things mentioned in these papers, as far as I am concerned, are common to diseases of the gastrointestinal tract.

I do not think that this is a logical way to approach this problem. Why do they not start out, as Alexander has pointed out, with the evacuation reflex, which in some way is associated with bowel training habits in childhood, and see if they cannot come up with a simple explanation. Of course, there are variations in individuals like there are variations in disease, but we as clinicians must begin to develop a basic foundation upon which we can build, and the myriad of information given us today leaves us just as much "up in the clouds" as we were before.

In my experience ulcerative colitis is the one disease which yields best to combined medical and psychotherapeutic approach, to the end that some permanency of cure can be established.

DR. MOSES PAULSON (Baltimore, Md.): Sixty cases of ulcerative colitis have been studied from the psychiatric standpoint by Dr. J. H. Conn and myself at The Johns Hopkins Hospital. They may be divided as follows:

1. The aggressive, peptic ulcer-like individuals with over-exaggerated ambitions;
2. The emotionally immature, dependent individuals who are closely attached to home and family;
3. The life long neurotic with over meticulous, perfectionistic behavior;
4. Individuals presenting mixtures of the above;
5. The relatively normal individuals with or without stress. This group never appears to be considered in association with this disease by our psychiatric colleagues.

In short, there is no specific personality type to be found in this disease.

Two additional facts stand out: first, that our psychiatric colleagues never present control studies. Without this, I cannot see how any evaluation regarding the specific role of the psyche in this disorder can be made. Secondly, since ulcerative colitis is relatively rare and these personality characteristics in the general population are so widespread, the most that one can say at this time, I think, is that these emotional factors aggravate the disease. However in certain individuals (neurotic characters) acute stress superimposed on chronic stress may be followed by ulcerative colitis. But even in this special group of susceptible individuals, the usual response under these adverse conditions is functional dyspepsia and other types of psychosomatic disturbances.

Finally, from the therapeutic standpoint, before we can give credit to intensive, prolonged psychotherapeutic care extending over several years, it must not be forgotten that in about 50 to 55% of the cases there are self-limited tendencies toward healing. These milder cases, not the severely intractable and the fulminating, are the ones usually referred for psychiatric aid. Besides, there are no adequate follow-up studies from a psychiatric standpoint. Psychiatric methods are helpful in giving

insight, adjusting the patient to his disease, alleviating anxiety and resolving conflicts. From this standpoint—treating the patient as well as his disease—psychotherapy has its place. Whether psychotherapy actually influences the cause of the disease, still remains a moot question.

DR. GEORGE GORDON MCHARDY (New Orleans, La.): At the San Francisco meeting of the American Medical Association, Dr. Donovan Browne, my associate, and I presented a study on the psychosomatic aspects of gastrointestinal disease. Dr. Sara Jordan, in her discussion, reversed the situation and, I believe, coined the word "somatopsychic." Since that occasion, I have been wholesomely impressed by the conclusions that one reaches in the study of disease appreciating the interplay of the psyche and soma in many entities. I often wonder, as a younger physician, if some of the intermediate men have not lost that great respect and awe for the art of medicine that the older man had in handling patients as individuals instead of disease entities. Just what part that altered attitude in medicine has contributed to the need for so much formal psychiatry I feel is apparent in these presentations.

I am sure, just as the two previous speakers have stated, that each of us here have personalities unto ourselves and I am sure that any of us sitting here, who had an intractable diarrhea or ulcerative colitis, would have a degree of anxiety sitting this long, and a degree of depression after we had left, over the fact that we would have to leave again shortly. I think that factor of interplay of psyche and soma is most important in disease, that the one is brought out by the other, and I feel that all of us and particularly the younger of us will do well to gain respect for the psychic element of disease and yet not forget that that part of the management is just a part of good medicine applicable by a competent internist.

DR. JOSEPH C. YASKIN (Philadelphia, Pa.): I regard Dr. Wolf's remarks as the greatest compliment in my 35 years of practice of medicine. I believe that psychiatric papers should be "business-like" in type. Often the psychiatric papers are not clear enough for the average medical reader.

The purpose of this paper was to bring order out of chaos. There is need for definitions of the terms that we use, and there isn't any doubt in my mind that a good many of the definitions given in this paper will not meet with the approval of psychiatrists and other clinicians. It is our hope that it is, however, the beginning of something concrete, and that eventually men all over the country will have the same meaning when they use a given term, so that we can be talking about the same thing at the same time. Eventually, something practical will emerge from this sort of approach.

Regarding Dr. Portis' remarks, I should like to emphasize that this report constitutes only the beginning of a long study. It is not intended as a final report. It is merely a small segment of a large circle. The personality study of our cases did not furnish us with a reason why the ulcerative colitis patient chooses the large gut instead of other organs in the body. Whether future studies will answer it, I am unable to state. The present study does not permit us to state that early bowel habits are

responsible for the development of ulcerative colitis. Based on my experience in neurology and psychiatry over a period of years, I have become less gullible in accepting convenient concepts and am less able to live in a false paradise.

I cannot answer Dr. Paulson. His experience with sixty cases is much larger than ours. On the other hand, based on an extensive study of our small series, I can state with reasonable certainty that each of the twenty cases was not an average normal individual as judged by the study of personality traits. We have established to our own satisfaction that these individuals were neurotic before they developed ulcerative colitis, and that their neurotic traits were not produced though they might have been increased by the pain, the diarrhea and embarrassment incident to the symptoms from which they suffer.

DR. ALBERT J. SULLIVAN (New Orleans): There was little discussion of my paper, but I should like to say a word or two about ulcerative colitis, and I should like to read a short quotation from the I Corinthians: 1-7, for what I think these patients need is best described by Paul.

"If I speak with the tongues of men and of angels, and have not charity, I am become as sounding brass or a tinkling cymbal.

"And if I should have prophecy, and should know all mysteries, and all knowledge, and if I should have all faith, so as to remove mountains, and have not charity, it profits me nothing.

"And if I should distribute all my goods to feed the poor, and if I should deliver my body to be burned, and have not charity, it profiteth me nothing.

"Charity is patient; is kind. Charity does not envy; is not pretentious; is not puffed up; is not ambitious; is not self-seeking; is not provoked, thinks no evil, does not rejoice over wickedness, but rejoices with the truth,

"Beareth all things, believeth all things, hopeth all things, endureth all things."

Now, Paul wasn't describing the patient with ulcerative colitis or he wouldn't have put that last clause in, "endures all things." Patients with this disease have learned to endure all sorts of measures, as we have heard today.

A METHOD FOR THE QUANTITATIVE DETERMINATION OF GASTRIC SECRETORY INHIBITION*

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I. INTRODUCTION

This investigation was undertaken in an attempt to develop a simple bio-assay procedure for the quantitative determination of gastric secretory inhibitors.

Studies on the inhibition of gastric secretion have been carried out for the most part in man, the dog and the rat and to a lesser degree in other animals. In man, the double histamine test has usually been employed to give a measure of secretory inhibition¹⁻³. Sometimes test meals have been used^{1, 4}. In the rat, the preparation most often employed is that developed by Shay and his associates in which pyloric ligation is performed and no other stimulus to secretion is given⁵⁻⁷. Most studies have, however, been made with the dog. In this animal, gastric secretion has been collected from the intact stomach⁸ by tubing or by drainage of pouches of part⁹ or all¹⁰ of the stomach. The secretory stimuli usually used have been histamine¹⁰ or a meat meal^{9, 11}. Histamine has been given as a double test¹² or in multiple doses over prolonged periods^{10, 13}.

After a review of these methods it was evident that those utilizing the dog possessed features which seemed to make this animal the most suitable test object. One objection to use of the dog is the comparatively large quantity of inhibitor which may have to be administered to obtain an effect in contrast to that which, for example, might be sufficient in the rat. In the dog, however, exact collections of juice from pouches of the entire stomach or portions of the stomach may be made and this allows precise appraisal of the temporal relations of the action of an inhibitor as well as an accurate estimate of the degree of inhibition it produces. Also the secretory mechanism affected by an inhibitor can be evaluated at least to some degree by selection of suitable stimuli. These considerations led us to select the dog as the test animal in the method to be described.

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Even in the dog, the variety of methods used to obtain samples of gastric juice and the different stimuli employed when testing inhibitor activity have made comparisons between the results of different authors very difficult.

Another factor which has made quantitative evaluation of data obtained on different dogs and from different authors difficult is a finding made by Gray, Bradley and Ivy¹⁰ during their study of the action of enterogastrone. They showed that the degree of gastric secretory inhibition produced by enterogastrone is dependent, in part at least, upon the rate of gastric secretion at the time of testing. This finding indicates that if repeatable quantitative determinations of gastric secretory inhibitor activity are to be based on changes in the production of gastric juice, then the rate of gastric secretion per unit of mucosa at the time of testing must be known or must be the same in all of the tests. Because of the difference in size of animals, in the size of their stomachs or in the size of pouches of their stomachs, it has been difficult to establish an identical rate of secretion per unit area of mucosa in all animals. We have developed the following procedure in an attempt to standardize some of these variables and thereby, we hoped, obtain a method which would yield repeatable quantitative determinations of inhibitor activity.

II. THE BASIC PRINCIPLE OF THE ASSAY PROCEDURE

Dogs with Heidenhain pouches are used. In each assay a rate of gastric secretion is used which represents a similar state of physiologic activity in the gastric mucosa of each dog. This is obtained by first determining the maximal rate of hydrochloric acid secretion possible from each pouch in response to histamine and then selecting a fixed percentage or proportion of this maximal rate for use during the determination of inhibitor activity.

III. TECHNICS EMPLOYED THROUGHOUT THE STUDY

The Heidenhain pouches were prepared with the animals under ether anesthesia, the usual aseptic surgical precautions being used. They were made through a left rectus incision, then brought to the midline and drained there by a vitallium cannula. With this technic, when the dog is in the standing position the pouch is drained from its most dependent portion and the complete collection of secretion is greatly facilitated. Because of early irregularities in secretion, it was found advisable to delay use of the animals for a postoperative period of at least three or four weeks.

Before carrying out tests, the animals were fasted for at least eighteen hours and fasting samples of gastric juice were collected for periods of fifteen to thirty minutes. If the fasting secretion contained acid equivalent to more than two or three drops of tenth-normal sodium hydroxide the animal was not used that day.

Histamine was used as the gastric secretory stimulant in all tests. The doses given in this report are expressed in terms of histamine base. The histamine was always dissolved in physiologic saline solution and administered subcutaneously every ten minutes.

Samples of gastric juice were collected regularly at fifteen-minute intervals. The volume of the juice secreted was measured, the acidity determined by titration with tenth-normal sodium hydroxide using dimethyl-amino-azobenzene as an indicator. The hydrochloric acid content of the sample of juice was calculated from this titration.

IV. DETAILS OF METHOD AND DATA UPON WHICH IT IS BASED

1. *Establishment of Maximal Rate of Gastric Secretion.*—Experience has shown that if the maximal output of hydrochloric acid from a Heidenhain pouch is to be obtained in response to histamine, the doses of histamine used in the initial injections should be small. As a routine the starting dose was 0.05 mg. repeated every ten minutes. As soon as secretion had reached a steady state in response to this amount of histamine, but not sooner than one hour, the dose given each ten minutes was doubled. Then, when the secretion had again reached a plateau, and again in not less than one hour, the dose was again doubled. This procedure was continued until doubling the dose of histamine no longer produced an increase in the output of hydrochloric acid (fig. 1). In many instances, the dose was increased until a decline in secretion occurred (fig. 2a). When the initial dose of histamine was 0.1 mg. or more per ten minutes or when the dose was increased more rapidly than once each hour then the secretory rates obtained were often less than those produced with smaller initial doses and less frequent increases in dose (fig. 2b).

In computing the results of such tests, either the values for the three fifteen-minute periods of greatest output of hydrochloric acid have been averaged to give the maximal rate of gastric secretion per fifteen-minute period for the particular day, or the values for the four consecutive fifteen-minute periods of greatest output of hydrochloric acid have been added to give the maximal rate of gastric secretion per hour for that particular day. Usually each test required five to seven hours for completion. When dogs were first used, at least 2 tests for maximal rate of secretion were made before assays of inhibitor action were performed.

2. *Variability of Maximal Rate of Gastric Secretion.*—The objective in each assay is to test for inhibitor activity while hydrochloric acid is being secreted from the Heidenhain pouch at a definite proportion of that pouch's maximum. This cannot be accomplished unless the maximal rate of secretion is sufficiently stable to allow it to be satisfactorily estimated on the day of the assay. While determinations of maximal output from a pouch show considerable variability

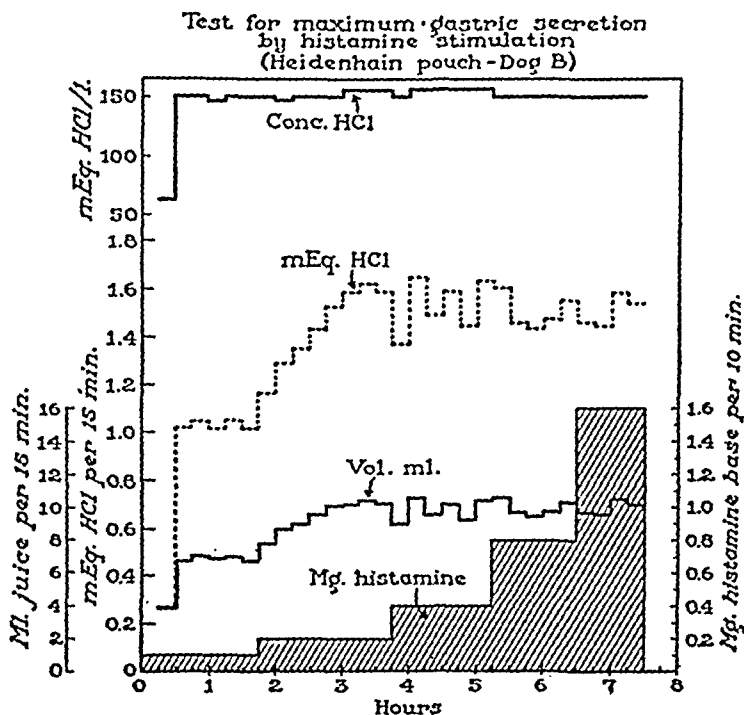


FIG. 1. Determination of the maximal output of hydrochloric acid from the Heidenhain pouch of dog B in response to histamine given subcutaneously every ten minutes. The maximum was attained when doubling the dose no longer increased secretion.

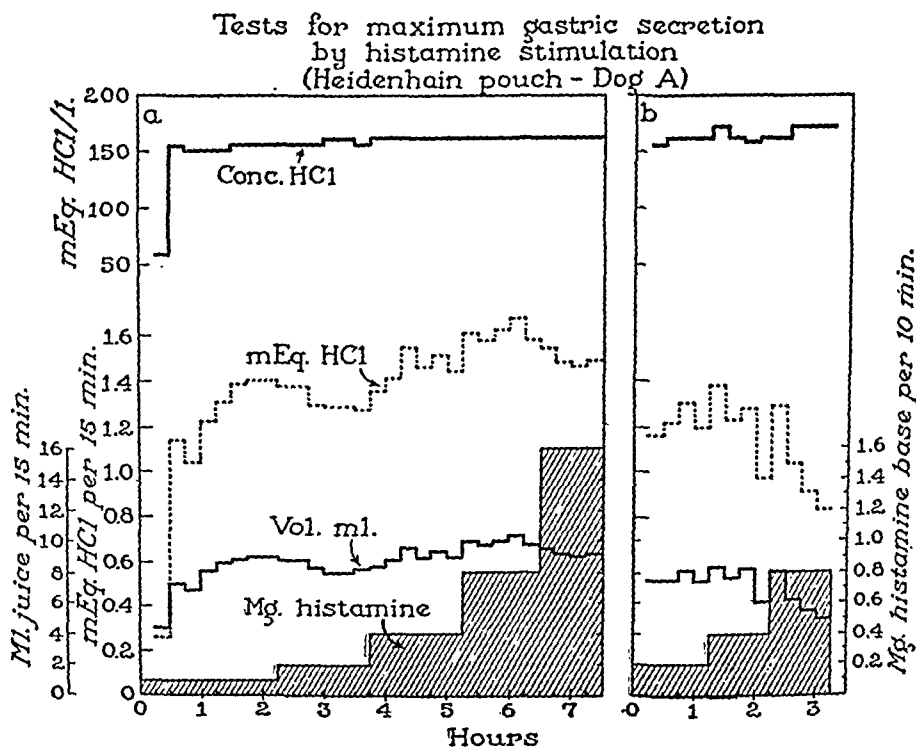


FIG. 2. Two attempts at determination of maximal secretory response of a Heidenhain pouch (dog A) to histamine given every ten minutes. *a*. Test was satisfactory; note decline of secretion at highest histamine dosage. *b*. Test was unsatisfactory, apparently because of initial high dosage.

(table 1), the changes in most animals are such that a sufficiently accurate estimate of the current peak output can be made to satisfy the requirements of the assay.

One estimate of variability found useful when considering a recent or new determination of maximal output has been the percentage change of this maximum from the mean of values obtained on preceding occasions. In a series of 13 consecutive dogs in which maximal outputs of hydrochloric acid were repeatedly determined during periods ranging from one to eleven months, 2 showed pronounced variability (dogs I and J, table 1). In the case of dog J the

TABLE 1

Seventy-eight Determinations of Maximal Gastric Secretory Response to Histamine From Heidenhain Pouches of 13 Dogs

DOG	TESTS	MONTHS OF OBSERVATION	MEAN MAXIMAL VOLUME, ML./15 MIN.	MAXIMAL MILLIEQUIVALENTS OF HYDROCHLORIC ACID PER 15 MINUTES			
				Mean	S.D.	C.V.*	Range
A	3	1	9.9	1.55			(1.47-1.63)
B	2	1	9.4	1.41			(1.18-1.63)
D	3	1	10.6	1.63			(1.47-1.72)
F	3	1	4.7	0.67			(0.62-0.73)
G	2	1	7.0	1.07			(1.04-1.10)
I†	7	3	8.1	1.20	0.38	32	(0.64-1.80)
J†	9	4	4.9	0.62	0.40	65	(0.00-1.29)
	6	5	5.7	0.77	0.10	13	(0.66-0.90)
K	11	11	7.9	1.17	0.20	17	(0.92-1.41)
L	11	10	8.8	1.29	0.22	17	(0.83-1.56)
M	4	2	9.7	1.45	0.21	14	(1.21-1.66)
N	4	2	11.0	1.62	0.12	7	(1.51-1.76)
O	6	2	5.6	0.79	0.19	24	(0.49-0.96)
Q	7	7	8.5	1.27	0.21	17	(0.98-1.60)

* C.V. is the coefficient of variability (standard deviation per mean times 100).

† Dog showed slow decline of maximal rates over last two months of observation during which period, however, assays were satisfactory.

‡ Maximal values showed great variability for four months during which assays were found unreliable. Later when maximal values became stable, assays gave repeatable results (fig. 3).

instability of maximal output was present for four of eleven months (fig. 3) and in the other dog, I, for two of a three-month period of study. During the period of extreme variability in dog J, 6 of 9 determinations of maximal output showed a change of more than 30 per cent over the mean of preceding values. Two assays of inhibitor activity made during this period at rates of secretion which were believed to be about half the maximum, produced much more pronounced inhibition than was obtained in identical assays on other animals whose maximal values of secretion were much more stable. In fact, as experience accumulated with this animal, it was temporarily outlawed as unsuitable for assay

purposes. Then, later when the maximal values stabilized (fig. 3), estimates of inhibitor activity became much more in keeping with those given by other animals and the dog was reinstated for assay purposes. Even with this stabilization, however, this animal has continued to be more sensitive than other animals used for testing inhibitor activity.

In dog I the maximal output of the pouch progressively declined during the last two months of a three-month period. However, throughout the three months only one of the tests for maximal output gave a value more than 30 per cent below the mean of earlier determinations and the assays made during the entire period were similar to those obtained from animals with stable maximal outputs of hydrochloric acid.

Maximal HCl outputs from Heidenhain pouch
(dog J)

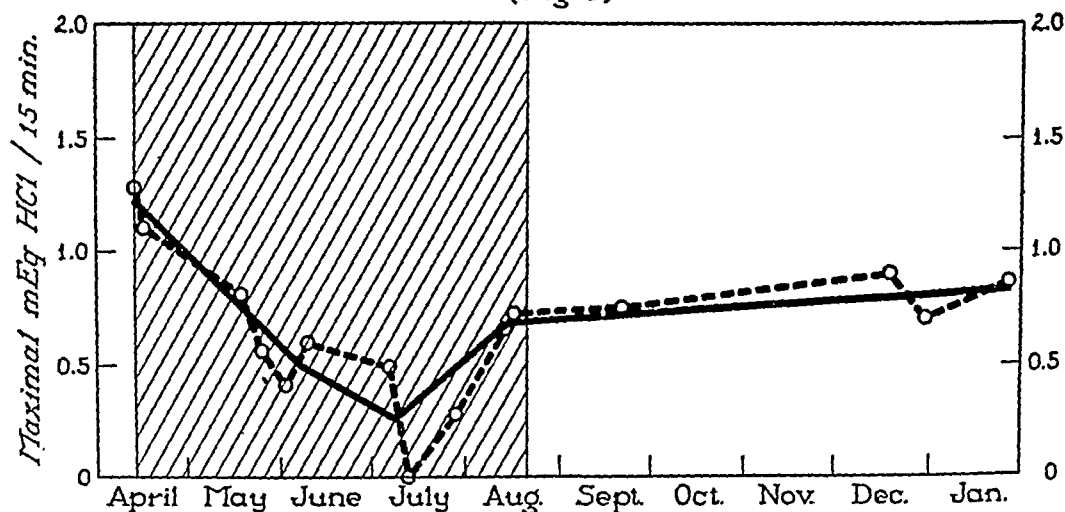


FIG. 3. Maximal outputs of hydrochloric acid from the Heidenhain pouch of dog J. The interrupted line joins consecutive determinations; the solid line indicates the approximate mean. During the period represented by the shaded area, assays of inhibitor action were unsatisfactory.

Other animals besides these 2 gave maxima in excess of plus or minus 30 per cent of the mean of preceding values. Fifty-six determinations have been made on the other 11 animals presented in table 1. Five of these animals have each had 1 estimate which exceeded the mean of their preceding values by more than 30 per cent. The greatest changes encountered in the series were a fall of 57 per cent and a rise of 43 per cent in the maximal values. In all but 2 of these instances, the determination was promptly repeated (at least one day's rest between tests was always allowed) and the value obtained upon repetition was always much closer to the mean of the preceding determinations. Such an occurrence and also the range of variability of maximal outputs of a more stable member of this group are shown graphically in figure 4. Experience with this

series of animals has led to the rough rule which we are currently following: if a determination of maximum in a dog differs from the mean of preceding values by more than 30 per cent, then the test is repeated; if the value obtained upon repetition continues to show variability of more than plus or minus 30 per cent then the animal is not used for assay purposes until the maximum has become more stable.

In the early stages of the development of the assay method, determinations of maximal rate were made every week or two. Then it was thought that the rate of secretion during the assay had to be a very exact proportion of the maximum. Later, when it was found that there was considerable tolerance in

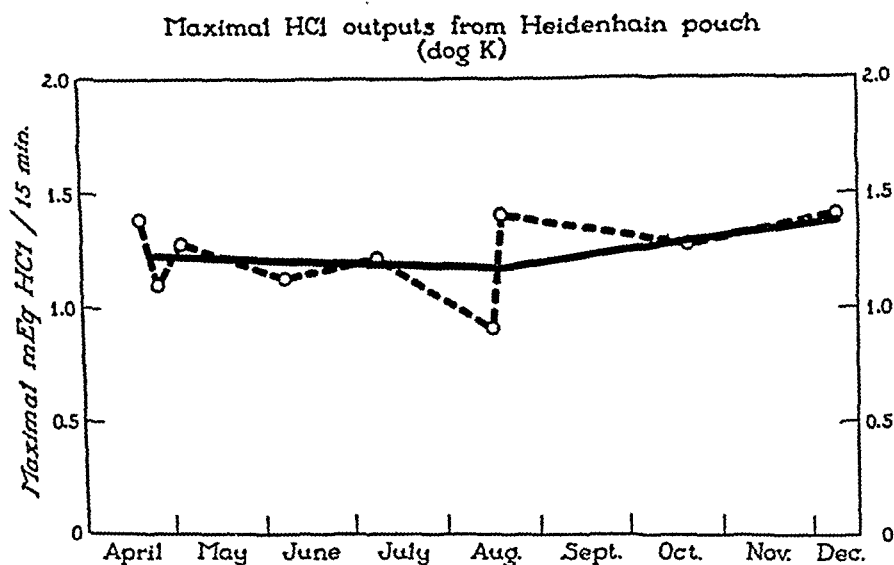


FIG. 4. The interrupted line joins consecutive determinations of maximal outputs of hydrochloric acid from the Heidenhain pouch of dog K. The solid line indicates the approximate mean. Assays of inhibitor activity were satisfactory throughout the entire period.

this regard, determinations of maximal rates were made at approximately monthly intervals. If, however, unexplained irregularities of secretion arose during tests, maximal rates were promptly checked. The impression has been gained that irregularities of secretion have been reduced in some animals by the provision of extra sodium chloride in the diet.

3. *Constancy of Gastric Secretion in Response to a Fixed Dose of Histamine.*—After establishment of the maximal output of hydrochloric acid from a pouch and selection of the percentage of the maximum to be used, the assay of inhibitor activity is then based on the assumption that when the dose of histamine which gives the desired rate of secretion has been found, the output of hydro-

chloric acid will remain constant for the period of the assay provided this dose of histamine is regularly injected and no other influences are brought to bear on the mucosa. This assumption has been put to test by determining whether or not the responses of Heidenhain pouches to fixed doses of histamine are sufficiently stable over periods of five or more hours to allow quantitative assay of inhibitor action.

TABLE 2

Hourly Outputs of Hydrochloric Acid From Heidenhain Pouches In Response to Fixed Doses of Histamine Given Every Ten Minutes

DOG	TEST	MG. OF HISTAMINE EVERY 10 MIN.	RATE OF SECRETION IN CONTROL PERIOD AS % OF MAXIMUM	MILLIEQUIVALENTS OF HYDROCHLORIC ACID, OUTPUT PER HOUR							RESULTS AS PER ASSAY PROCEDURE		
				1st	"Control" period		4th	"Test" period		7th	Hydrochloric acid/hr. in milliequivalents during		Per cent change
					2nd	3rd		5th	6th		Control period (2nd & 3rd hr.)	Test period (5th & 6th hr.)	
A	1	0.025	51	2.3	3.1	3.2	3.6	2.8	3.0	3.1	3.2	2.9	-9
A	2	0.03	59	2.7	3.5	3.8	3.9	3.6	3.4	—	3.7	3.5	-5
B	3	0.025	23	1.3	1.3	1.2	1.7	2.1	1.9	1.6	1.3	2.0	+54
B	4	0.05	41	1.7	2.0	2.5	2.4	2.7	3.3	3.0	2.5*	3.2*	+28
C	5	0.025	10	0.9	0.8	0.7	0.6	0.4	0.6	0.7	0.8	0.5	-38
C	6	0.05	38	2.2	2.8	2.9	3.0	3.0	3.0	—	2.9	3.0	+3
D	7	0.05	58	2.0	3.7	3.9	4.1	3.4	3.4	2.5	3.8	3.4	-11
E	8	0.05	26	0.6	1.6	1.7	1.8	1.8	1.8	1.7	1.7	1.8	+6
K	9	0.02	30	1.5	1.3	1.3	1.4	1.5	1.5	1.2	1.3	1.5	+15
K	10	0.06	48	0.6	1.7	2.2	2.3	2.4	2.2	—	2.2†	2.3	+5
L	11	0.07		0.7	2.2	3.1	3.5	3.4	3.2	—	3.1†	3.3	+6
L	12	0.025	42	2.0	2.3	2.1	2.2	2.0	1.9	1.9	2.2	2.0	-9
J	13	0.05	61	0.4	1.7	1.6	1.6	1.6	1.6	—	1.7	1.6	-6
Q	14	0.07	50	0.5	2.4	3.0	2.9	2.8	2.5	—	2.7	2.7	0
U	15	0.08	49	1.1	1.9	2.1	2.2	1.9	1.8	—	2.0	1.9	-5

* Third and fourth hours used as control, and sixth and seventh hours as test periods.

† Third hour used as control since secretion had not reached steady state until then.

Histamine was given subcutaneously every ten minutes for periods of six or seven hours in a series of 15 tests on 10 dogs. The dose of histamine given with each injection was unaltered throughout a test. From previous experience with the dogs, it was anticipated that the amounts injected would produce hydrochloric acid outputs of 60 per cent or less of the maximum.

The results of all of the tests are shown in table 2. For purposes of comparison, the data have been computed as though an actual assay had been in progress. In some tests an injection of physiologic saline solution was given at the end of a mock control period. This was done because most of the animals had been used previously in inhibitor assays and the injection served to deter-

mine whether there was any possible release of inhibitor influences through psychic or conditioned reflex channels.

In all but 3 tests the secretion had built up to a plateau at the end of the first hour and the second and third hours could be used as a mock control period with which to compare the hydrochloric acid outputs of the remaining hours. In the exceptions, secretion did not reach a steady state soon enough to allow use of the second hour. Actually, in a true assay the control period is determined when it is evident that a plateau of secretion has been reached irrespective of time. While this usually occurs within one hour, sometimes, as in these instances, it takes longer. One test was continued long enough to allow use of the third and fourth hours for the control period (dog B, test 4); in the other instances this was not so and the third hour alone has been used for comparison with the later periods. In an actual assay in which changes in secretion are likely to occur as a result of the action of an inhibitor such a short cut is not advisable. Two hours are usually required for reasonable certainty that a plateau of secretion has been reached.

Also, in accord with the procedure usually adopted in an assay, the hydrochloric acid outputs of the fifth and sixth hours have been averaged and the percentage change of this mean from the mean hourly output of the control period has been calculated. Expressed in this fashion three test periods differed from their respective control periods by more than plus or minus 20 per cent. Two of these were obtained during observations on dog B. This dog was not used in assays because of this pronounced variability and because of difficulty in obtaining satisfactory tests of maximal rates. The third test was made at a rate of secretion which was only 10 per cent of the maximum (dog C, test 5). This experience and others involving very slow rates of secretion have led us to abandon the routine use of secretory outputs of 15 per cent or less of the maximum in the assay procedure. All the values obtained in the other 12 tests are within a range of plus or minus 15 per cent. The tests indicate that in most dogs, secretion of hydrochloric acid from Heidenhain pouches in response to fixed doses of histamine given every ten minutes remains sufficiently constant over periods of six or more hours to allow estimation of inhibitor activity.

4. *The Rate of Gastric Secretion to be Used in the Assay of Inhibitor Activity.*—As stated in the introduction, Gray, Bradley and Ivy¹⁰ showed in 1937 that the degree of inhibition produced by enterogastrone in the secretion of juice from pouches of the entire stomach of dogs was dependent, in part at least, upon the rate of secretion from the pouches at the time of testing. To check this observation in dogs with Heidenhain pouches and to determine the most satisfactory secretory rate to be used in assays of inhibitor activity the following series of tests was made. A standard fixed dose of a potent gastric secretory inhibitor was first given to a series of 3 dogs when these dogs were secreting hydrochloric

acid from their pouches at rates which were nearly maximal, one-half maximal and one-fourth maximal. The results obtained were then checked in 4 other tests. The inhibitor used was a preparation of hog gastric mucus* which had been previously tested by two of us and found to possess a high degree of in-

TABLE 3
Effect of Standard Dose of Inhibitor on Different Rates of Gastric Secretion*

DOG	CONTROL SECRETORY RATE AS % OF MAXIMUM	PER CENT INHIBITION			
		1st hr.	2nd hr.	3rd hr.	Mean 2nd & 3rd hr.
I	113	52	65	75	70
L	109	79	59	41	50
K	87	75	66	54	60
Mean.....	103	69	63	57	60
L	55	90	81	54	68
K	47	63	60	39	50
I	42	71	60	58	59
Mean.....	48	75	67	50	59
L	25	76	100	100	100
K	25	87	100	100	100
I	20	97	100	100	100
Mean.....	23	87	100	100	100
Check determinations					
K	55	80	65	40	53
J	71	85	74	64	69
Mean.....	63	83	70	52	61
I	39	86	95	97	96
J	29	96	100	100	100
Mean.....	34	91	98	99	98

* Preparation of hog gastric mucus kindly provided by Armour Laboratories, Armour & Company, Chicago, Illinois.

hibitor activity¹⁴. The dose employed was 10 mg. per kilogram of body weight.

The results are given in table 3. When the control rate of gastric secretion was 40 per cent or more of the maximum the inhibition produced was 50 to 70 per cent (mean 60). When the secretory rate was close to one fourth of the

* We are indebted to Dr. J. H. Glynn of the Armour Laboratories, Armour and Company, Chicago, Illinois, who kindly provided us with the preparation of hog gastric mucus used in this study.

maximum, inhibition was 100 per cent, the secretion of hydrochloric acid being stopped by the injection of the inhibitor.

The results indicate that the sensitivity of the secretory process to inhibitor action is much greater when the rate of hydrochloric acid output at the time of testing is less than 40 per cent of the maximum. At rates of secretion in excess of 40 per cent of the maximum, inhibitor action was quite constant, apparently being unaffected by increases of rate from one-half to full maximum. Insufficient tests have been made to determine whether the inhibition produced increases gradually as the secretory rate of the test declines below 40 per cent or whether a sharp and sudden increase in sensitivity occurs at a critical level of secretion. In this regard the 2 tests done on dog I at 42 and 39 per cent of maximum may be misleading. They gave 59 and 96 per cent inhibition, respectively. It is unlikely that a decline in the test rate of secretion from 42 to 39 per cent of maximum was responsible for this pronounced change in inhibitor effect. This animal had, at the time of these tests, a declining maximal output of hydrochloric acid and it is more likely that the estimates of maximum used in the tests were in error.

As a result of these tests two assay procedures have been adopted. In the first, inhibitor action is tested while hydrochloric acid is being secreted by the pouches at rates of 50 per cent or more of their maximal outputs. Rates of 45 per cent of maximum are usually accepted for the test but rates of 40 per cent of maximum place such a high degree of reliability upon the determination of maximum that they are not used if accuracy in the test is needed. As a rule rates of one-half maximum or more are used. At these rates responses to fixed doses of histamine are quite constant (see previous section) and repeatable quantitative determinations of inhibitor activity have been obtained.

The second procedure is used when small amounts of inhibitor activity are anticipated and a higher degree of sensitivity in the test is needed. The inhibitor is titrated at rates of gastric secretion ranging from 20 to 30 per cent of the maximal rate. Rates somewhat beyond these limits have been used, particularly if quantitation was not an important requirement. Assays at these slower secretory rates provide a delicate test for the detection of inhibitor activity. At these levels, however, secretion often shows greater spontaneous variability than at the faster rates used in the first procedure. Although insufficient tests have yet been done to determine the point exactly, it seems likely that the increased sensitivity in the second procedure is accomplished at the expense of considerable reliability.

V. APPLICATION OF THE METHOD TO THE DETERMINATION OF GASTRIC SECRETORY INHIBITORS

The assay procedure has been employed satisfactorily for quantitative determinations of the gastric secretory inhibitor activity in preparations of

enterogastrone, urogastrone and extracts of gastric mucus. In addition, it has been employed to test, in a quantitative fashion, the inhibitor effect of a variety of circumstances. Detailed presentation of these results belongs in other reports by other authors and for this reason an example only is given here.

Two of us have made an extensive study of the gastric secretory inhibitor effects of preparations of hog gastric mucus available commercially as hog gastric mucin¹⁴. One batch, kindly provided us by Dr. J. H. Glynn of Armour Laboratories, was tested on 17 occasions, various doses being used. In each test the animals were secreting gastric juice at rates which were one half or more of

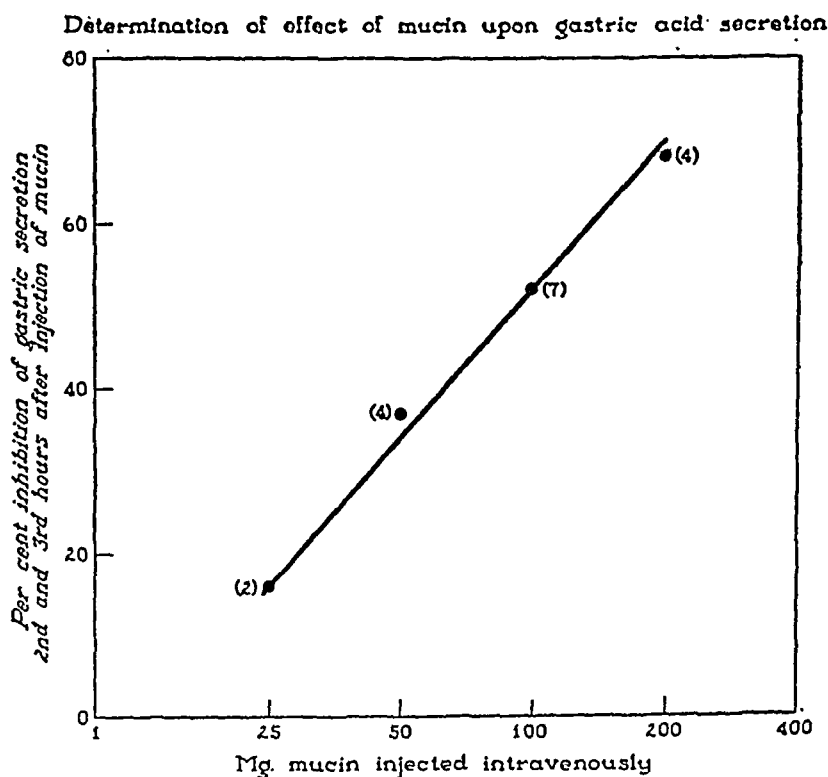


FIG. 5. Repeated quantitative determinations of the gastric secretory inhibitor action of a preparation of hog gastric mucus (commercially known as hog gastric mucin). The mean inhibition produced by each dose is plotted against the dose on a logarithmic scale. The numerals in parentheses are the number of tests done at each dosage level.

the maximum. The results are illustrated in figure 5 in which the percentage inhibition is plotted against the dose of mucin with the latter on a logarithmic scale. The quantitative relationship found was better than expected. It certainly would not have been as linear if fewer determinations had been made. The results serve to illustrate that the method yields satisfactory quantitative determinations of gastric secretory inhibitor activity.

COMMENT

Extensive studies of gastric secretory inhibitor substances have been made by using dogs with pouches of the entire stomach. We have adopted the use of

the Heidenhain type of gastric pouch because in our hands dogs with such pouches have been much easier to maintain in a constant state of good health than those with pouches of the entire stomach. Placing the pouch in the midline position so that it drains easily when the dog stands and the use of vitallium cannulae have improved the performance of our animals to the point where consistent collections have been obtainable over periods of many months. Only 2 dogs of a series of nearly 20 showed progressive declines in outputs of hydrochloric acid in response to histamine. In one the output returned, after a period, to its previous level and the dog was then used successfully for assays; in the other, although the maximal output declined over a period of two months, assays of inhibitor activity were satisfactory. A third animal, the second tested in the series (dog B), showed such irregularities in secretion that it could not be used in the assay procedure. Apart from these 3 all the other Heidenhain pouches so far tested have been uniformly satisfactory for assay purposes.

Histamine was used as a stimulus to gastric secretion in preference to a meal because inhibition of the secretory response to a meal could be due to the interruption of motility and digestion in the gastro-intestinal tract without a direct effect of the material tested on the secretory mechanism in the gastric mucosa. The inhibition of the gastric secretory response to histamine indicates, rather more strongly, at least some action at the gastric mucosa and thus carries with it an element of specificity which may be lacking in the inhibition of prandial secretion.

Continuous secretion of hydrochloric acid in response to histamine was adopted in the assay in preference to the double histamine technic because in the latter the effect of an inhibitor may be missed or poorly quantitated if the onset of action of the inhibitor does not happen to coincide with the secretory response to the second histamine injection. Testing the action of an inhibitor against a constant continuous secretion of hydrochloric acid allows appraisal of the temporal relationships of the action of the inhibitor which may be undetected in the double histamine test and in the duodenal ligation test in rats.

Our observation that the degree of reduction of gastric secretion produced by an inhibitor is at least partly dependent upon the rate of secretion at the time of testing confirms in general the earlier finding of Gray, Bradley and Ivy¹⁰. It is interesting that the amount of inhibition produced by a fixed dose of an extract of gastric mucus was unaffected by changes in rate of secretion once the rate was in excess of 50 per cent of the maximum. Whether or not this would be true of other inhibitors has not been established in this study. Our observations on the constancy of secretion from Heidenhain pouches in response to histamine given every ten minutes are also in accord with the results of similar tests done by Gray, Bradley and Ivy¹⁰ in dogs with pouches of the entire stomach.

The maximal gastric secretory responses obtained in dogs by Hanson, Gross-

man and Ivy¹⁵ are not directly comparable to those obtained in this study because they used intact dogs and dogs with pouches of the entire stomach while we used Heidenhain pouches. At present we have no physiologic explanation to offer for the differences in sensitivity of these preparations to histamine.

It is not claimed that the assay method presented in this report is better than other procedures which have been used in the past. Such comparisons have not been made. The procedure selected in any study will depend upon the type of information sought. The method is offered because it has been found useful in following, in a rough quantitative fashion, the gastric secretory inhibitor effects of a variety of extracts and of a variety of circumstances. It is hoped also that it will aid in the further elucidation of the mechanism of action of gastric secretory inhibitors.

SUMMARY

A method for the quantitative determination of gastric secretory inhibitor activity has been developed. Dogs with Heidenhain pouches are used. Histamine is used as the gastric secretory stimulant. It is given subcutaneously every ten minutes. Quantitative determinations of inhibitor effects are made at fixed rates of secretory activity. Similar fixed rates of secretory activity in all pouches are obtained by first determining the maximal output of hydrochloric acid from each pouch in response to histamine and then by conducting the assay of inhibitor activity at a definite proportion of this maximum. Tests showed that rates of secretion of 50 per cent or more of the maximum are reduced to a similar extent by identical doses of inhibitor; the same doses of the inhibitor produced, however, much more pronounced effects on rates of secretion of about one fourth of the maximum. Based upon this finding, two procedures are suggested: one in which inhibitor action is tested against rates of secretion of 50 per cent or more of the maximal rate, and a second more sensitive procedure in which the secretory rate used is in the neighborhood of one fourth of the maximal rate.

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DISCUSSION

DR. F. HOLLANDER (New York City): We are indebted to Dr. Code and his associates for the development of a laboratory procedure for evaluating the efficacy of various inhibitory substances. It is evident from what he said today, I think, that the gastric mucus and commercial mucin preparations which he used may give rise to inhibitory effects, measured by this method, for any of three reasons: 1. There may be a specific inhibitory substance present in the secretion; 2. The inhibitor may be a degradation product of the native secretion, and to that extent an artefact; or 3. The inhibitor may be some substance present in the mucus but only fortuitously associated with it—that is, derived from some other source.

I think it is important to bear these several alternatives in mind and I, for one, will await further reports on results of this work with much interest.

DR. MORTON I. GROSSMAN (Chicago, Ill.): I wish to make two very brief comments on Dr. Code's important paper. First, in regard to the basic assumption concerning the relationship between the rate of gastric secretion and the per cent of inhibition that is produced by a standard dose of inhibitor, I should like to point out that in Dr. Code's procedure two things were being varied simultaneously, namely, dose of histamine and the rate of gastric secretion. In our studies we found there is a much better correlation between the dose of histamine and the per cent of inhibition than the rate of secretion and the per cent of inhibition, and when the dose is kept constant, then we do not get a good correlation between the rate of secretion and the per cent of inhibition.

This is an important point, and must be cleared up in order to establish a reliable assay method.

The second point concerns the relationship between the degree of pyrexia, and the per cent of inhibition. The hourly time course of these two phenomena was not parallel, as Dr. Code has pointed out; however, when crystalline pyrogens derived from bacterial sources are used to produce inhibition of gastric secretion, the same lack of correlation can be noted. Therefore, failure of the time course of pyrexia and inhibition to coincide does not rule out pyrogens as the cause of the inhibition.

DR. CHARLES F. CODE (Rochester, Minn.): I am in complete agreement with Dr. Hollander. We do not know what this material is. It comes down when mucus is precipitated. Its association with mucus may be purely fortuitous.

A crude preparation has been given orally by one of the members of our group. It was given by mouth to two dogs and its effect tested on the secretion in a separate pouch. The secretion of the pouch was apparently unaffected. There are obvious

defects to this experiment. The inhibitor placed in the pouch itself might have had some effect. Also, the crude material contains a good deal of protein; an active compound separated from protein might have been effective. From these remarks I am sure it is apparent that I would like to join those who discussed this paper in awaiting further evidence before deciding upon the mode of action of this inhibitor.

(Slide, figure 5 in paper) This slide illustrates the correlation between inhibitor action and the dose of the inhibitor when the method of assay employed throughout the study is used. The per cent inhibition produced is plotted against the dose in milligrams on a logarithmic scale. The straight line obtained indicates the satisfactory correlation and quantitation obtained by the method.

Regarding the use of a fixed dose of histamine in each assay: We have found considerable day to day variability in the response of pouches to fixed doses of histamine. In the assay method we have used we have attempted to reproduce a similar state of activity in the gastric mucosa each day and the yardstick we have employed has simply been the per cent of the maximum rate of gastric secretion. I agree, however, with Dr. Grossman that further data regarding this point are needed. I can simply say that with the method we are using this type of dose response is obtained (illustrated on slide, figure 5 in paper).

Case Reports

JULIAN RUFFIN, M.D.

Durham, N. C., Associate Editor in Charge

THE GRADUAL EVOLUTION OF ACUTE INFECTIOUS (EPIDEMIC) HEPATITIS INTO POST-HEPATIC CIRRHOSIS

CASE REPORT: H. H., CASE No. 461472

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PAST HISTORY

Onset of illness was in late July, 1943 (17 years of age), with nausea, anorexia, asthenia. About six weeks after the onset painless jaundice of slight degree developed; there was no history of use of alcohol or of hepatotoxic drugs; there had been no preceding transfusions of blood or plasma and no preceding acute illness. In December, 1943, patient entered a Detroit hospital because of the above symptoms; the physical examination was reported to have shown slight icterus, slight enlargement of the liver, but no enlargement of the spleen.

Laboratory reports: The Wassermann was negative; the blood count was normal, and no anemia was present until one month later; the agglutination with *Leptospira icterohaemorrhagica* was negative; the red blood cell fragility was normal; the icterus index varied between 10 and 30 units; the oral hippuric acid test revealed 1.8 grams excretion; the bromsulphalein revealed 35% of dye retained in 30 minutes and 30% in 60 minutes; the biliary drainage revealed large clumps of white cells present, a large amount of mucus, but no crystals were found; oral cholecystography revealed poor visualization of the gallbladder.

The symptoms persisted, under treatment, during the next 6 months.

In August, 1944, patient entered a well-known university hospital for further evaluation and advice. A diagnosis of biliary cirrhosis was made, apparently based upon the persistence of slight jaundice, anorexia and malaise, associated with enlargement of the spleen, as well as the liver, but with no evident ascites at that time, and the fact that the patient was a young girl.

Laboratory reports: The bromsulphalein revealed 70% retention (time not reported); serum albumin was 2.9 grams per cent; and the blood platelets were reduced.

Patient was placed upon intensive liver therapy and numerous blood transfusions with no appreciable improvement during the following 12 months. In spite of multiple liver extract injections and blood transfusions the hemoglobin in July, 1945, was 49%; the red blood count was 1,690,000; the blood platelets 57,400; and the blood prothrombin 70%.

(8) There were transient periods of a day or two of chills, fever and malaise during 1946 particularly, occurring every two to three months. (9) Patient's general health was fairly good, otherwise, during the last two years of life. (10) Terminal illness was very acute and fulminating and lasted only a little more than a week. It was preceded by a week when patient was persuaded by a diet faddist to reduce protein and carbohydrate in the diet. (11) This patient's life was maintained for $4\frac{1}{2}$ years only by the most intensive sort of treatment.

DISCUSSION OF DIAGNOSIS AND TREATMENT

A. Diagnosis: (1) The early development of an enlarged liver, with definite impairment of liver function as indicated by tests with development of enlargement of the spleen about 12 months after the onset of the illness justifies the diagnosis of hepatic cirrhosis. (2) Since there was slight jaundice present during much of the first 2 years of illness and no evidence of ascites during that period, the diagnosis of a hypertrophic type of biliary cirrhosis, made during the second year of illness, had some supporting evidence. (3) However, the appearance of ascites at the beginning of the third year of illness and the absence of jaundice during the third year with only slight and occasional jaundice during the fourth year, point to the presence of a portal type of cirrhosis. The decrease in the size of the liver during the fourth year is also typical of the later stages of portal cirrhosis. (4) Certain features of the total illness, however, are not satisfactorily explained by uncomplicated portal cirrhosis, but would be best explained by the associated existence of an acute infectious hepatitis which became chronic and led to the development of portal cirrhosis. The following facts about this patient's illness would thus be particularly well explained by an associated chronic infectious hepatitis: (a) The prodromal 45 day period of nausea, anorexia and asthenia before the first appearance of jaundice. (b) The degree of malaise and anorexia existing throughout the first two years of the illness. (c) The rather marked impairment of liver function at the very onset of the illness. (d) The degree and persistence of secondary anemia during the last 3 years of illness. (In the average case of portal cirrhosis the secondary anemia is not so extreme and therapeutic problem is not so momentous as here). (e) The periodic attacks of chills and fever and malaise, otherwise not explained, suggest repeated flareups of the liver disease. These exacerbations are known to be typical of chronic infectious hepatitis which persists after the acute phase. (f) The very acute fulminating terminal illness, occurring after the patient had been very well and lasting for only a little more than a week, suggests a toxic necrotic process within the liver parenchyma. *B. Treatment:* (1) This patient apparently did not receive any intensive liver therapy during the first five months of illness, before anemia and enlargement of the liver developed. (2) Every patient with acute infectious hepatitis, and every patient with cirrhosis

of the liver, should receive intensive liver therapy early, to prevent the development of more marked pathology, if possible, and, in case of acute hepatitis, to prevent an acute process from becoming chronic and progressive. (3) Liver function tests should be performed during the course of such treatment to demonstrate the course of the disease and the results of such treatment.

ABSTRACT OF SIGNIFICANT AUTOPSY FINDINGS

Case No. 461472, H. H.

Skin: Dark tan colored. Sclerae: Icteric. There are numerous striae over abdominal wall on either side. Liver: Extends 1 cm below right rib margin. Heart: Weighs 330 grams. Valves and myocardium are intact. Lungs contain excess frothy yellow fluid. Spleen weighs 1020 grams, measures 23 x 14 x 5. Section shows greyish red, homogeneous pulp. Liver weighed 1700 grams and measures 17 x 24 x 10. The surface is yellowish tan in color. The left lobe is enlarged out of proportion to the right. The lower third of the right lobe and $\frac{1}{2}$ of the left lobe are the seat of a massive, fibrous scar, the surface of which is depressed, smooth and firm for the most part. The remaining portions of the lobe are roughly nodular with deep crevices between the nodules. Cut surface shows the scarred area very firm and fibrous with only small scattered areas of liver parenchyma. A portion corresponding to the nodular parts is composed of rounded masses of liver parenchyma in which no normal architecture can be observed. Gastrointestinal tract: Stomach dilated, lumen contains 500 cc of clotted blood and 300 cc of fluid blood. There is a small bleeding point 4 mm in diameter near the cardia. Gallbladder contains very thick viscid bile. Adrenals: Weigh 19 grams each. Kidney architecture appears normal. Final anatomical diagnoses: (1) Chronic epidemic hepatitis in the stage of scarring and fibrosis. (2) Hemorrhage from gastric varices. (3) Pleural effusion. (4) Splenomegaly. (5) Ascites. (6) Pulmonary edema with early bronchial pneumonia.

COMMENT

The presence of large depressed fibrous scars in both the right and left lobe of the liver, coupled with the large regenerated nodules of parenchyma, suggest strongly that this is a case of chronic epidemic hepatitis with scarring and fibrosis, especially in the absence of any evidence of syphilis, which is the other disease involving the liver which might produce such large, localized lesions.

the aberrant pancreatic group and the adenomyoma group. In the former, the lesion was composed of typical adult pancreatic tissue with or without islets of Langerhans. In the latter, the duct structures closely resembled pancreatic and bile ducts and might represent displacement of the latter during development. The muscular elements may be an integral part of the nodule or merely represent residual or hypertrophied muscle of the gastro-intestinal tract. When present in the pylorus, these nodules may give rise to obstruction. They may be recognized roentgenographically as a polypoid tumor of the stomach or duodenum. At operation, the aberrant tissue may suggest a diagnosis of malignancy.

The pathogenesis of these lesions is reviewed by Clark³, King and McCallum¹ and Troll⁵. There are three theories of origin of heterotopic tissue: 1) It is due to transplantation of tissue from the original site during the embryonic state, either because of inflammatory or nonspecific intraperitoneal adhesions, or the occurrence of additional anlage. 2) Its presence is due to metaplasia of tissue during embryonic or postnatal life. Occurrence of an inflammatory reaction lends support to this hypothesis. 3) It is an atavistic phenomenon, or reversion of pancreatic tissue to a more primitive phylogenetic type, such as is seen in certain lower animals and fishes. In these species pancreatic tissue is diffusely scattered through the liver, peritoneum and muscular coats of the intestinal wall.

SUMMARY

1. The occurrence of two separate foci of pancreatic tissue in the gastric wall is reported.

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TETANY FROM SMALL BOWEL RESECTION AND SMALL AND LARGE BOWEL EXCLUSION

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Resection of the small and large bowel of varying degree may or may not be followed by tetany. There are but three instances reported in which tetany developed following such a procedure,¹⁻⁴ whereas there are many reports in which tetany did not occur following this procedure.^{7-10, 12-16} The following report is of a patient who developed tetany after a minimal resection of small bowel and an extensive shortcircuiting operation which excluded a large portion of both small and large intestine.

Case Report: W. G., a 17 year old white male who had an appendectomy with complicating peritonitis twelve years ago, was admitted to the hospital January 7, 1947 with abdominal pain and continuous vomiting of one week's duration. His last bowel movement was four days prior to admission. Examination revealed lower abdominal tenderness with absent peristalsis. A diagnosis of intestinal obstruction was made. After adequate restoration of fluid balance, a laparotomy was performed. A gangrenous loop of ileum was found as well as numerous adhesions. The involved portion of ileum measured 40 cm. and was resected over a Mukulicz clamp. Nineteen days later, an anastomosis between the resected loops of ileum was carried out and an ileostomy was done proximal to the anastomosis. Leakage was noted at this time from the anastomotic site and the bowel had to be trimmed frequently before an adequate anastomosis was made. After this operation, a Harris tube (single barrelled tube with a mercury bag at end) was inserted. Nine days later, drainage was noted from the wound, but it could not be determined whether this was coming from the ileostomy or the anastomotic site. Twelve days after the second operation, two fistulous tracts were noted. Twenty-eight days later, the mercury bag of the Harris tube had forced itself through the anastomotic opening and into the incision. A third operation was then performed and the end of the tube was located in the anastomosed area. In this region, the ileum was transected, both ends were turned in and an ileocolostomy was performed. Since the bowel was so matted together, it was impossible to determine how much small bowel was excluded. The patient recovered and was discharged on the 72nd hospital day.

He was next seen about one year later, on March 28, 1948, in a state of tetany. "Painful spasms" of the fingers and toes with accompanying numbness and tingling were present for two weeks before admission. He had been having three to four pasty and foamy stools daily since discharge from the hospital about one year ago. He also noted within the past two weeks that his scar was swelling and a yellowish material was exuding. Several injections of calcium had been given intravenously during the two week period before this admission on an out-patient basis.

receiving the medication described above. His weight was 112 on admission and 114 on discharge. He was discharged after 37 days with the above described regimen and has been doing fairly well since then, for a period of thirty-two weeks. On his last visit to the out patient department, thirty weeks after discharge, the serum calcium was 6.9 mg. % and he was only taking calcium as needed for his pares-thesia. Further reconstructive surgery is being contemplated.

DISCUSSION

This is obviously an instance of disturbed calcium metabolism due to deficient gastro intestinal calcium absorption. Calcium is absorbed chiefly from the upper portion of the small intestine. Its absorption depends on three factors—namely the hydrogen ion concentration of the contents of the gastro intestinal tract, the amount of phosphates and fat in the diet and the presence of vitamin D⁵.

Since calcium salts are relatively insoluble in alkaline media, their absorption is greatly enhanced by the addition of acidifying salts such as ammonium chloride. Since calcium is absorbed in the duodenum before the gastric juice is neutralized, the pH of the duodenum plays an important role⁵.

Calcium absorption is also controlled by such factors as an increased amount of phosphate present in the gastro intestinal tract. When accompanied by a low calcium intake, the phosphate forms an insoluble calcium salt, thus preventing absorption of calcium. Magnesium and potassium in excess also inhibit the absorption of calcium. Disturbances of fat absorption and increased fat excretion result in the formation of insoluble calcium soaps which are eliminated in the feces⁵. Other controlling influences are exercised by the serum proteins, parathyroid glands and kidneys.

In the case reported in this paper, there is obviously one factor which has not been mentioned and that is the limited absorptive surface area which consisted of only four to six feet of small intestine and less than half of the large intestine. The fat in this patient's diet was also not completely absorbed. This resulted in the elimination of foamy, light colored, pasty stools indicating the formation of calcium soaps with poor calcium absorption. Although fecal fat and calcium studies were not done on this patient, West et. al.¹, and Todd et. al.², showed that in their case (the same patient for both groups of authors) with only three feet of small intestine, 80% of the stool consisted of fatty acids and the ratio of fecal fat to fecal calcium was constant, indicating that the loss of calcium could be accounted for because of the formation of insoluble calcium soaps. Their studies also showed that the carbohydrate was almost completely utilized while about 25% of the protein and 45%–55% of the fat was lost in the feces¹. About 25% of the caloric value of food was thus lost, according to their calculations.

The results of these biochemical studies and our own clinical observations

in this case indicate that a diet high in carbohydrate and protein but low in fat should be used in treating cases of tetany due to extensive bowel resection. The diet should also contain large amounts of calcium, especially calcium chloride⁶ and a proportionately lower concentration of phosphorous, magnesium and potassium. An acidifying salt should be used to promote the absorption of calcium. Vitamin D should also be replenished preferably in a non-oily form (Drisdol). At present, there are several water soluble and injectable vitamin D preparations available. Paregoric and belladonna are useful in delaying transport and thus allowing for further absorption.

Several other studies have also been done on patients with resections. Haymond⁷ noted that of 1,161 cases, the total average length of the small intestine was 21½ feet or 657 cm. The metabolic studies showed that in cases where over 380 cm. of small intestine were resected, there was a definite abnormal loss of nitrogen in the stool. An excessive amount of fat was seen in cases where as little as 225 cm. were resected but no tetany was reported. The gastro intestinal series showed the head of the barium column in the rectum in four to eight hours. Diarrhea was the most common disturbing complication. This latter observation is confirmed by several writers^{4, 8} who also noted that there develops an increased diameter of the remaining bowel as a result of massive resection of small bowel or as a result of colectomy or colonic exclusion. Whitaker and Bargaen⁴, who described the latter groups, noted a decrease in the calcium level post-operatively, which except for two cases of tetany, returned to normal in one month. One of the cases of tetany had ulcerative colitis. Schneider¹¹ found a marked increase in urinary calcium excretion in colectomized dogs. This reveals that some factor in the colon is related to calcium metabolism as well.

In the case described here, the patient had both a large amount of small intestine excluded as well as over half of the large intestine so that both the factors of calcium absorption from the small intestine and the colon played a part.

SUMMARY AND CONCLUSIONS

1. A case of tetany resulting from a resection of the small intestine with extensive small bowel and colonic exclusion is reported.
2. The treatment of the case herein described consisted of a low fat high protein and high carbohydrate diet, large doses of calcium, acidifying salts, soluble vitamin D, vitamin B complex, tincture opii and bismuth subcarbonate.
3. A brief review of calcium metabolism and its relation to gastro-intestinal surgery is presented.
4. Close post-operative observation of the calcium level of patients who have undergone extensive small and large bowel surgery is indicated.

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Editorial

SOME CONDITIONING FACTORS IN NUTRITIONAL DISEASE

For years it has been becoming more and more apparent that malnutrition may be caused by a number of factors other than an inadequate dietary intake. Anything that interferes with the absorption or utilization of nutrients or that increases their requirements or their destruction or their excretion may cause trouble. These conditional factors, as Jolliffe called them, are all likely to precipitate nutritional deficiencies when the person is on a diet that would otherwise be adequate if the disturbing factor had not become operative.

In *Physiological Reviews* for January, 1948, there is a splendid article by Benjamin H. Erschoff, who has brought together all the available information on this subject. The work was undertaken in co-operation with the Committee on Food Research of the Quartermaster Food and Container Institute for the Armed Forces.

Some of the factors which cause trouble are strong physical exertion, fever, the taking of drugs, the coming into the body of toxins, deleterious effects from bad environment, mental conditions, pregnancy, lactation, hyperthyroidism and anything which raises the metabolic requirements of the body. There is a bibliography of 457 titles.

[W. C. A.]

Comments

Readers are invited to contribute to the Comment Section of Gastroenterology short notes expressing their opinions on controversial topics and matters of current general interest.

PSYCHOSOMATIC ASPECTS OF DIGESTIVE DISORDERS

In the course of many diseases the digestive tract is so influenced by the nervous system that some physicians and laymen have come to consider nervousness as the cause of the disease.

Thus, if a person who has a highly susceptible nervous system has a peptic ulcer, cholecystitis, pancreatitis, regional enteritis or one of the many forms of ulcerative colitis, it is easy to assume that nervous tension has caused the disease. More careful analysis would probably show that there was more than one cause of the disease to be considered.

Some men will also observe a difference in the nervous reactions of the patient with a peptic ulcer and the one with ulcerative colitis. In the case of peptic ulcer a single ulcer has developed because of certain acid, pepsin and mechanical factors. All of these factors are affected by the nervous make-up of the patient. On the other hand, the patient who has ulcerative colitis, has, instead of one ulcer, myriads of ulcers of the large intestine. In his case, the infectious phase is the major one, and, in so far as the origin and inception of the disease are concerned, the individual's nervous make-up probably does not play a part. Yet, once the disease is well established, nervous tension and anxiety materially influence the patient's progress. In some mild forms of the disease, when only short segments of the large intestine are involved, for example, the rectum, unusually pleasant experiences may have a salutary effect upon the progress or control of the disease.

However, this does not offer any suggestion about the etiology of ulcerative colitis. To treat properly patients who have colitis, the fact must be accepted that a variety of infectious diseases may be present, some of which can be devastating not only to the intestine and the system in general but also to the morale of the patient. It is common knowledge that disease above the diaphragm makes for optimism and below the diaphragm for pessimism, and ulcerative colitis of the streptococcal variety, exemplifies this dictum superbly.

What has been said about ulcerative colitis, applies in a measure also to other infections which affect the digestive tract, such as cholecystitis, pancreatitis and regional enteritis. The degree of severity of the psychic impact

on patients with these diseases varies directly with the amount of the digestive tract involved, and is greatest when the distal segments of the large intestine are affected. This is exactly as would be expected, for the physical disability of the patient also varies in the same manner.

Unfortunately, various functional disorders of the intestines, caused largely by nervous upsets, are frequently confused with real inflammatory conditions. Thus patients with the irritable bowel syndrome are often led to believe that they have colitis, since patients with both conditions may have diarrhea. The physician who has been consulted by a patient with diarrhea will want to distinguish clearly between the two conditions by means of appropriate examinations and laboratory investigations. Once the diagnosis is made, the degree of nervous impairment responsible for the patient's disability should be determined and adequate management should follow.

As a rule the program of management readily divides itself into two phases; (1) combating the intestinal or other infection directly and vigorously with suitable diet, drugs and antibiotics, and (2) helping the individual bear his disability. The latter problem will at times be the largest one. Occupational and physical therapy may be helpful. The use of mild sedatives and antispasmodics finds a place in this program. Many of these patients are troubled by insomnia, inability to rest, and by indigestion and intestinal hypermotility. Small amounts of phenobarbital and bellafoline, such as exist in *Belladanal*, are admirably suited to this purpose. One-fourth to one-half tablet taken by mouth before meals and at bedtime has a soothing effect on the irritability of these patients and tends to quiet the overactive digestive tract. Thus, it is well to give this drug to patients who have peptic ulcer, ulcerative colitis, the irritable bowel syndrome and other forms of intestinal unrest.

Psychiatric consultation will be indicated only for the most refractory conditions or in those cases in which the disordered nervous mechanism has assumed major proportions. Cases of this type rarely occur.

The importance of the psychosomatic phase of digestive disorders has been greatly overemphasized. This does not minimize the importance of treatment for this phase of any given digestive disorder. The psychosomatic phase, however, should not be considered etiologic in cases of inflammatory lesions of the intestinal tract. Treatment should be directed to both the nervous influences, and the local disease.

J. ARNOLD BARGEN

PROTEIN DEFICIENCY IN PEPTIC ULCER PATIENTS

The new section headed "Comments" with its italicized invitation is too tempting to resist, especially upon reading the Editorial in the June, 1949 issue entitled "Protein Hydrolysates in the Treatment of Peptic Ulcer." My comment will not be concerned with the discussion of the value of protein hydrolysates, but solely with a statement in the conclusion of this Editorial: "There is no definite evidence that protein deficiency is a usual accompaniment of peptic ulcer. . . ."

In addition to the surgical complications of peptic ulcer which I commonly see and in which several types of protein deficiency are frequent, there is also, in my opinion, considerable clinical evidence that many non-surgical patients with peptic ulcer suffer tissue protein deficiency. This may not be true in certain clinics; nevertheless, there are many ulcer patients throughout the country still subsisting on milk and cream diets containing but 20 to 30 grams of protein per day. Objective evidence that this is true was furnished by the data of Kenamore and his coworkers, to which reference was made. The significance of this study lies in the observation that large amounts of nitrogen were retained on a high nitrogen intake in a series of ulcer patients who were presumably on a good ulcer diet and who had lost no weight and showed no hypoproteinemia. This, of course, was not due to the use of protein hydrolysates—the same degree of positive nitrogen balance would undoubtedly have occurred if whole protein food were used. Indeed, in a similar study by T. S. Sappington, who presented his findings before the Association, high degrees of nitrogen retention were also observed in patients with ulcerative colitis when they were placed upon a high protein intake of normal foods. These patients, too, showed no obvious evidence of protein deficiency although definite symptomatic improvement seemed to follow the high protein intake. Observations by William D. Robinson of the University of Michigan, unpublished but described to the author, seem to have a similar implication. This observer increased the protein intake of a number of medical students. In some of them the output of nitrogen immediately increased so that balance was established at once at a higher level. A number of them, however, retained much of the ingested nitrogen for several days, reaching an equilibrium only within a week. This difference may also be due to a similar tissue protein deficiency in the latter cases, subclinical in degree, but metabolically significant.

The important point to emphasize in these studies is the probability that all of the individuals retaining large amounts of nitrogen were suffering from a tissue protein deficiency—else why would they have held on to so much of the ingested nitrogen? Until these findings are explained in another way, they must be accepted as evidence that tissue protein deficiency may occur in many

patients in the absence of measurable hypoproteinemia or significant loss of weight.

To quote again from the Editorial "An adequate intake of protein can be achieved easily, physiologically and relatively inexpensively by a proper intake of food." To this all readers would subscribe wholeheartedly; yet we cannot complacently assume that this end has been achieved. It is my firm belief that with careful observation and scrutiny many patients including ulcer patients will be discovered in whom a proper intake of food has been the exception rather than the rule.

ROBERT ELMAN, M.D.

Book Reviews

CYBERNETICS OR CONTROL AND COMMUNICATION IN THE ANIMAL AND THE MACHINE.
Norbert Wiener. The Technology Press. John Wiley & Sons, Inc. New York.
1948. pp 194. Price \$3.00.

Occasionally a book appears which marks a new era in science, and this is one of them. It is of great interest to every research worker if only because it shows how closely inter-related all branches of science now are. In many institutions efforts are made to keep every specialist within the bounds of his specialty or even within a small part of it. This book shows how foolish this policy is. The more a man roves through the fields of science, searching for information and technics which will throw light on his own problem, the more valuable he is.

The word cybernetics is derived from a Greek word meaning a helmsman. Norbert Wiener is professor of mathematics at the Massachusetts Institute of Technology. Some years ago he belonged to a club of young scientists who met to discuss their problems. At these meetings Wiener discovered that he, with his mathematical and electrical technics, could throw light on the physiologist's problems, and they could give him ideas for devising huge electronic ultra rapid calculating machines.

Wiener was one of the first men to work on the problems of developing these calculators, and soon he saw analogies between these machines and brains. He saw, for instance, that the all or none character of the discharge of a neurone is analogous to the single choice made in determining a digit on the binary rather than denary scale used in the machines. The synapse which so interests physiologists today is a mechanism for determining whether a certain impulse will serve as an adequate stimulus for the discharge of the next neurone, and this sort of thing has its counterpart in the computing machines. As Wiener says, the vocabulary of the engineers building these machines soon became contaminated with the terms of the neuro-physiologists and the psychiatrists!

In the winter of 1943 to 1944, the need for gathering together physiologists, engineers and mathematicians interested in these common problems became so apparent that a meeting was held. One of the men, Dr. Rosenbluth, a professor of physiology, saw that light could be thrown by the calculating machines on epileptic convulsions and on auricular fibrillation. The physiologists and Dr. Wiener saw also that an intention tremor can easily be produced by a failure of adjustment in the feed-back system such as controls the rudders of huge trans-Atlantic liners. This feed-back control mechanism is now used in many machines. Today the scanning mechanism which is the basis of television is also throwing light on the anatomy and physiology of the visual cortex. Light has been thrown by the new calculating machines on the alpha rhythm in the electroencephalogram.

It is suggestive that at times the big electric calculators seem to "go crazy" and as Wiener says, then the thing to do is either to take away all work from them and

give them a rest, or to send a strong electric shock through them! They sometimes behave like a fibrillating heart!

The engineers, who built the calculating machines, had to build a mechanism for memory into them, and their experience is now helping the physiologist to understand how human memory may work.

Wiener points out that more and more machines are now being developed which can do nearly all of the things that men and women formerly did in factories. Already some large factories are being run by only a few men and many photoelectric cells and other controlling and checking machines. Today pick and shovel laborers, even at starvation wages, could not compete with a steam shovel as an excavator, and the time will soon come when the average human being of mediocre attainments will have little to sell in the way of abilities that will be worth anyone's money to buy. As Wiener said, this may or may not be a good thing. He is a mathematician and not a sociologist.

Psychologists must now get interested in cybernetics because it is obvious that the structure of that huge calculating machine which is the brain of man must, in an individual, determine what it can and will do during life. The question then is, to what extent can a man alter the workings of the machine with which he was endowed at birth? Can he by self-education so rebuild or enlarge the machine or alter the settings as to get decidedly different results out of it?

Very interesting is the suggestion made by the electrical engineers that, as the brain ages, it gets more and more difficult for the person to break into the storage circuits containing memory. The clinician sees this phenomenon in persons with cerebral arteriosclerosis. When perhaps an old friend drops in, the man, with great effort, can be himself for awhile, but later it is too much effort and he slumps into apathy.

Work on the electrical calculating machines is throwing light also on the way in which an overload on the human nervous system can suddenly produce a breakdown.

Altogether, this is a book to read more than once, and ponder over. Much of it is too full of calculus for anyone but a mathematician to understand.

THE ACUTE ABDOMEN IN RHYME. Zeta. H. K. Lewis & Co. Ltd., London, 1949, pp. 93.

This book is ascribed to Zachary Cope, the prominent abdominal surgeon. It is curious how some persons can write in rhyme about as easily as they can write in prose. As Zeta says, "The use of rhyme in teaching is quite small, Its limitations great and plain to all. But use it has, although it may be merely, To put some things more quaintly or more clearly. Of course the thing may not appeal to you—A rhyme gives not to surgery its due! A serious subject needs a solemn style, A lighter method may arouse your bile! Well, wait and see, at least this I can state, A rhymster needs to think and concentrate. . . . My aim, which well may be I shall not reach, Is to amuse you while I try to teach."

The book is full of useful information. Those who like rhyme and a touch of humor will be pleased with it.

CANCER OF THE ESOPHAGUS AND GASTRIC CARDIA. *George T. Pack*. The C. V. Mosby Company, St. Louis, 1949, pp. 192.

Dr. Pack has edited a valuable book on the treatment of cancer of the esophagus and the cardia. Most of the chapters have been written by different men. They describe the modern methods by which efforts are now being made to save patients with what was formerly an inoperable lesion.

LES PROBLÈMES DU TRAITEMENT DES ULCÈRES PERFORÉS GASTRO-DUODÉNAUX. *J. Milaret and G. Edelmann*. Masson et Cie., Paris. pp. 134.

This little monograph of 134 pages is concerned with the problems of the acutely perforated ulcer and the complications that can follow this accident. It contains a lot of information on the subject.

A TEXTBOOK OF NEUROPATHOLOGY. *Ben W. Lichtenstein, M.D.* W. B. Saunders Company. Philadelphia. 1949. pp. 474.

This is a splendid piece of work, well written and well illustrated. It was written primarily for the medical student and for those persons who are undergoing training in neurology, psychiatry, pathology and neurologic surgery.

Dr. Lichtenstein is associate professor of neurology at the University of Illinois College of Medicine.

ABSTRACTS OF CURRENT LITERATURE

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STOMACH

ARCHER, V. W. AND COOPER, G., JR. Pyloric obstruction more accurately demonstrated by food-barium mixture. *Am. J. Roent. Rad. Therapy*, 60: 593 (Nov.) 1948.

Attention is called to the fact that the rate at which the stomach empties a barium-water mixture is not an accurate index of the rate at which it can empty food. When the pylorus and duodenum are of normal caliber, though the initial rate of emptying is slowed down, only an occasional stomach will show a significant increase in the amount of gastric residue 6 hours after a barium-food mixture. When the lumen of the pylorus or duodenum is reduced in caliber, it is necessary to use a barium-food mixture to determine accurately the rate at which a stomach empties. This determination is of value in helping to decide whether to relieve surgically a pyloric or duodenal constriction. It is suggested that vagotomy for relief of duodenal ulcer should be combined with gastroenterostomy when there is a significant 6-hour barium-food retention before operation.

FRANZ J. LUST

CRIDER, R. J. AND WALKER, S. M. Physiologic studies on the stomach of a woman with a gastric fistula. *Arch. Surg.*, 57: 1 (July) 1948.

This article reports the first recorded observations on the interior of the human stomach in woman. A 21-year old Negress sustained a stricture of the esophagus from the accidental ingestion of lye. Subsequently, a gastrostomy opening was made which later became infected and broke down. There resulted a 6 cm. opening of the stomach lateral to the left rectus muscle.

The following observations were made:

(1) A cyclic motility of variable magnitude and intervals was noted within the stomach and the cardia. (2) Two types of contractions were seen, a basic kneading action and a peristaltic action. (3) Anger, resentment, fear and anxiety were associated with decreased motility and secretion of the stomach, with blanching of the mucosa. This is in contrast to the hypersecretion and hypermotility response noted previously in these situations. (4) Menstruation and sleep had no appreciable effect on the stomach behavior. (5) Mechanical stimulation in the region

of the cardiac sphincter resulted in heartburn, nausea, retching and a reflux of bile-stained secretion. (6) Painful stimuli caused a pronounced increase in motility but little effect on secretion or on color gradients.

MARCEL PATTERSON

CRIDER, R. J. AND WALKER, S. M. Effect of intravenously administered amino acids on the stomach of a woman with a gastric fistula. *Arch. Surg.*, 57: 10 (July) 1948.

Gastric function was observed in a young woman with a large fistula which permitted direct observations of the interior of the stomach. The present study was done to evaluate the effects of various intravenous fluids on the stomach. The intravenous injection of 5 per cent hydrolyzed protein ("Amigen") in 5 per cent glucose with 2 gm. of sodium chloride, resulted in cessation of motility and decrease in secretion with no appreciable change in acid content but with a decrease in pepsin content. Crystalline amino acids in 5 per cent dextrose intravenously produced similar effects. No changes were observed during the injection of 10 per cent dextrose in water, 10 per cent dextrose in water to which was added 2 gm. of sodium chloride, or isotonic sodium chloride solution.

It is concluded that the intravenous injection of amino acid mixtures depresses gastric function and thus promotes gastrointestinal rest.

MARCEL PATTERSON

MARVIN, C. P. AND WALTERS, W. Leiomyosarcoma of the stomach. *Arch. Surg.*, 57: 62 (July) 1948.

Sixteen cases of leiomyosarcoma of the stomach are reviewed with a report of a case of multiple leiomyosarcoma. This rare tumor is usually seen in younger age groups than is carcinoma. Three cardinal findings suggest the diagnosis: (1) Gastrointestinal hemorrhage (in 69 per cent of the cases, this was the presenting symptom); (2) epigastric distress or pain in the left upper abdomen (50 per cent of the cases), and (3) the presence of a mass in the upper abdominal area (44 per cent). Loss of weight, nausea and vomiting are not frequent symp-

toms. Anemia and free hydrochloric acid in the stomach are usually noted. The tumor may be found endogastrically, intramurally or exogastrically. A gastric filling defect, a central niche and fistulae in the lesion may be suggestive of leiomyosarcoma. The exact diagnosis is rarely made roentgenologically. Treatment consists of surgical removal, as these tumors are not radiosensitive. The prognosis is better than for carcinoma of the stomach. The majority of the lesions are of low grade malignancy with late metastasis.

MARCEL PATTERSON

ROACH, J. F., SLOAN, R. D., AND MORGAN, R. H. The detection of gastric carcinoma by photofluorographic methods. Part I. Introduction. *Am. J. Roent. Rad. Therapy*, 61: 183 (Feb.) 1949.

It has been shown statistically that cancer of the stomach is a prevalent and rapidly fatal disease for which the only promising form of therapy, available to-day, is surgery. If surgery is to be successful, resection must be done early in the course of the disease, prior to the appearance of symptoms. Thus, methods must be developed whereby large segments of the population may be examined at regular intervals to find the asymptomatic but positive cases. The most feasible method for carrying out this sort of an examination is the photofluorographic process used by the authors. A pilot study has been established to determine the efficiency of this method using the male outpatient population of the Johns Hopkins Hospital, above the age of forty. The study will be pursued for 5 years.

FRANZ J. LUST

ROACH, J. F., SLOAN, R. D., AND MORGAN, R. H. The detection of gastric carcinoma by photofluorographic methods. Part II. Equipment design. *Am. J. Roent. Rad. Therapy*, 61: 188 (Feb.) 1949.

Photofluorographic equipment is described by which roentgenographic examination of large population groups for gastric carcinoma may be carried out with the application of little more radiation than that employed in conventional roentgenography. The appara-

tus uses a Patterson type E-2 screen and a Schmidt camera. The grid-screen-camera assembly is mounted beneath a horizontal roentgenographic table to permit the examination of patients in the recumbent position. Films are taken in the antero-posterior and right anterior oblique position after the ingestion of a small amount of barium, and in the postero-anterior and right oblique position after ingestion of a large amount of barium. In each case, two views in the right anterior oblique position are taken to demonstrate the progress of peristalsis.

FRANZ J. LUST

SANCHEZ-PALOMERA, E. AND WANGENSTEEN, O. H. Production of irritative and destructive changes in the gastric mucosa followed by regeneration. *Proc. Soc. Exp. Biol. Med.*, 70: 427 (Mar.) 1949.

The gastric mucous cells of cats and dogs were stimulated by placing various substances into the stomach with both ends ligated. Mustard oil; clove oil, from 0.5 to 2% in corn oil; and eugenol, in watery solutions up to 10%, were used. The animals in one group were sacrificed 3 to 10 hours following operation. In another group, the ligatures on the stomach were removed after exposure to the irritant, the stomach emptied, and the wound closed. The same procedure was repeated 2 or 3 weeks later. Biopsies were taken before and after completion of the experiment. In the group of surviving animals, biopsies were also taken 24 to 48 hours after stimulation was stopped. The action of the irritants on closed loops of small bowel and colon was studied also.

In the colon, depletion of the goblet cells was readily produced. Diminution of the number of goblet cells was obtained in the small bowel. In the stomach profuse macroscopic secretion of mucus was obtained with no obvious histological change. When the stimulation was stronger or the period of application increased, necrosis of the mucosa occurred. The small bowel was the most susceptible and the stomach quite resistant to the irritative action. Edema, hyperemia, extravasation of red blood cells and leukocytic infiltration were noticed first. Later on, the most superficial portions of the epithe-

lium were destroyed; the exposed cells of the stroma disintegrated. Cellular debris and mucous covered the mucosa, and apparently acted as a protective covering and prevented necrosis of the walls of the pits. Further action of the irritant caused a progressive destruction of the remaining mucosa until ulceration occurred. In the stomach deepening of the foveolae was first observed. Later the most superficial segments of epithelium became detached, leaving only the deepest portions of the foveolae. If irritation ceased at this stage, immediate regeneration took place. Under a protective layer of debris and mucus, proliferation started at the bottom of the gastric pits. Growth of the cells from these areas restored the continuity of the surface epithelium, however the mucosa looked thinner thereafter. If destruction had not reached the bottom of the pits, it was followed by complete regeneration of the epithelial continuity in less than 48 hours. This protective mechanism, the "mucous barrier", may be of greater importance in the pathogenesis of gastric ulcer than previously considered.

H. NECHELES

JENKINSON, E. L. AND HAMERNIK, F. J. Roentgenologic deformities of the pyloric portion of the stomach with absence of surgical and pathological findings. *Radiol.*, 51: 798 (Dec.) 1948.

The authors describe several cases in which the roentgenological examination of the stomach showed a deformity of the pyloric portion of the stomach. None of these patients had a malignancy, even though the roentgenological aspect simulated this disease. Adhesions after gall bladder operation, adhesion of the omentum, were mostly the cause for this deformity. In one instance, even the laparotomy did not reveal the cause for the deformity of the antrum. After operation, the same appearance of the pyloric region was seen.

FRANZ J. LUST

WOOD, I. J., DOIG, R. K., MOTTERAM, R. AND HUGHES, A. Gastric biopsy—Report on fifty-five biopsies using a new flexible

gastric biopsy tube. *Lancet*, 25: 18 (Jan.) 1949.

The authors describe a flexible biopsy tube with which 55 biopsies of the stomach have been obtained without any undue pain or bleeding. Adequate specimens can be obtained to be sectioned and stained according to orthodox histological methods. The obvious limitation of the procedure is that the specimen is obtained blindly, and selective biopsy is not possible. Its greatest value lies in cases of diffuse lesions of the stomach.

PHILIP LEVITSKY

BOWEL

WEINTRAUB, S. AND WILLIAMS, R. G. A rapid method of roentgenologic examination of the small intestine. A preliminary report. *Am. J. Roent. Rad. Therapy*, 61: 45 (Jan.) 1949.

The authors' technique for hastening examination of the small intestine involves the following: (1) Roentgenoscopic and roentgenographic examination of the esophagus, stomach and duodenum using 4 oz. of barium and 4 oz. of normal saline at room temperature; (2) patient drinks 8 oz. of ice cold normal saline; (3) 14 by 17 inch abdominal film is taken five minutes later; (4) patient drinks a second 8 oz. of ice cold normal saline immediately after the five-minute film; (5) 14 by 17 inch films are taken at 15 and 30 minutes; (6) all three abdominal films are shown "wet" to the roentgenologist who roentgenoscopes and takes spot films of suspicious areas; (7) if the head of the meal has reached the cecum, this is done also for the terminal ileum—if not, additional films are taken at half hour intervals until it has. The roentgenologist then roentgenoscopes and takes spot films as indicated.

In 90 per cent of the 87 normal cases studied with this method, the barium meal reached the cecum in one hour or less. The entire small intestine was delineated satisfactorily, and the normal mucosal pattern was not disturbed. In 17 cases in which lesions were present, they were demonstrated equally as well with this method, and in some cases better than with the hourly technique.

FRANZ J. LUST

MICHEL, M. L. AND McCAFFERTY, E. L. Acute obstruction of the colon. *Arch. Surg.*, 57: 774 (Dec.) 1948.

The mortality in 103 cases of acute colonic obstruction studied was 29 per cent. This series included only the most common causes, namely—carcinoma, diverticulitis and volvulus. The age of the patient, the fact that 70 per cent of the cases had an acute obstruction resulting from neoplasm, and the failure by the physician to recognize the condition sufficiently early, all constitute extreme liabilities.

Acute obstructions of the small and large bowel must be differentiated because errors in treatment are caused by failure to do so. Small bowel obstruction is due usually to postoperative adhesions or hernial complications, and intubation may, therefore, be indicated. In the colon obstruction, however, such treatment may lead to fatal delay. On the other hand, immediate resection of the large bowel will lead to disastrous results. Alterations in the blood chemistry occur very early only in small bowel obstruction and leukocytosis develops late. Once the differentiation has been made, one should not wait for the classical clinical picture of large bowel obstruction to develop, for early surgery gives by far the best results. If the exact location or cause of the obstruction is in question the left lower quadrant should be explored. Transverse colostomy for left, and ileo-transverse colostomy with cecal decompression for right, colonic lesions are recommended procedures.

Diagnosis is facilitated and usually exact with barium enema. Barium should not be administered orally. To improve the present mortality rate, the recognition of an acute surgical emergency is necessary. Limitation of surgery to decompression is urged, for conservative therapy or radical immediate resection can be equally disastrous.

A. I. FRIEDMAN

HAYES, M. A. Chronic ulcerative colitis and associated carcinoma. *Am. J. Surg.*, 77: 363 (Mar.) 1949.

The author cites several articles which present suggestive evidence that inflammatory processes in the large bowel may pre-

dispose to benign and malignant tumor formation. Because of the chronicity and severity of the inflammatory process in chronic ulcerative colitis, the colon seems particularly susceptible to malignant degeneration in this disease. The malignancy which develops may be either a localized polypoid carcinoma or a diffuse carcinomatous involvement of almost the entire inflamed area. Most observers agree that the prognosis is especially grave and that radical treatment is rapidly indicated when carcinoma of the colon is superimposed on chronic ulcerative colitis.

The incidence of carcinoma of the colon among all admissions to three hospitals is reported as 0.88, 0.5, and 0.3 per cent respectively; whereas the incidence of colonic carcinoma superimposed on a previous ulcerative colitis is 2.5 per cent (800 cases), 1.6 per cent (185 cases), and 0.7 per cent (451 cases) respectively in the same institutions.

Three cases of chronic ulcerative colitis complicated by carcinoma of the colon and resulting in death are also reported. Constant vigilance of the colitis patient by barium enema and proctoscopy is the author's advice.

NATHAN SHAPIRO

AULT, G. W. Surgical treatment of ulcerative colitis. *Arch. Surg.*, 58: 243 (Mar.) 1949.

This report deals with the indications for surgery in patients with idiopathic ulcerative colitis. Twenty-three patients received surgery in a group of 120 with ulcerative colitis. The specific indications for surgical intervention are deemed to be: (1) constitutional and visceral degenerative changes; (2) anorectal complications; (3) polypoid degeneration and carcinoma; (4) obstruction and tumor mass; (5) perforation, abscess and fistula; and (6) segmental ulcerative colitis.

The author prefers not to do surgery in the presence of hemorrhage, acute fulminating ulcerative colitis and initial acute perforation into the free peritoneal cavity.

LEMUEL C. MCGEE

GASTER, J., DAVIS, H. A., PRIETEL, P. A., AND MARSH, R. L. Extent of strangulation

of the small intestine compatible with life. *Arch. Surg.* 58: 312 (Mar.) 1949.

This paper reports an effort to reproduce experimentally the sudden loss of blood supply to a segment of the intestine, such as exists in acute mesenteric thrombosis or embolism, in strangulated intestinal obstruction and in stab wounds of the mesentery. Rabbits had the blood supply removed by cutting and ligation of vessels to segments of intestine from 5 to 13 cm. in length. When 5 cm. of intestine was devascularized, the tissue maintained viability presumably by the blood entering through the intramural channels from each end of the segment. With segments of 6 and 7 cm. if survival occurred, the blood supply of the segment came from adhesions and growth of new vessels. When larger segments were deprived of blood supply, gangrene and death was the usual result.

LEMUEL C. MCGEE

FICK, K. A. AND WOLKEN, A.P. Necrotic jejunitis. *Lancet*, 256: 519 (Mar.) 1949.

The onset of necrotic jejunitis is usually acute with violent upper abdominal pain in the epigastrium, a little to the left of the mid-line. Nausea and vomiting accompany the pain. Circulatory collapse is striking and may cause death within 24 hours. There is a slight rise in the temperature, the sedimentation rate is elevated, and the leucocyte count is increased. The abdomen presents a reflex rigidity of the left side with hyperesthesia. If the acute stage is survived, the patient enters a subacute stage with the picture of ileus, or enteritis with blood-stained diarrhoea. The primary pathologic finding is a localized necrotic inflammation of the jejunum. More than one area may be affected, and the disease can involve the ileum and even the colon. The mucosa becomes necrotic and the process can penetrate the wall of the intestine setting up a peritonitis. The etiology is unknown. The authors believe that it is a specific infective disease possibly due to an anerobe related to *Cl. Welchii*. Treatment should be conservative and supportive in the milder cases. In the severe cases, surgical procedures, such

as resection or exteriorization, should be adopted.

PHILIP LEVITSKY

LIVER AND GALL BLADDER

DOUGLASS, T. C. AND CUTTER, W. W. Arterial blood supply of the common bile duct. *Arch. Surg.*, 57: 599 (Oct.) 1948.

The authors observe that there have been few reports of anatomic studies on the blood supply of the common bile duct. Fifty human postmortem specimens (arterial trunks) were injected with a red synthetic latex. After clearing the tissues the vessels could be visualized. Abundant anastomotic loops similar to those seen in the arterial supply of the intestinal tract were found in 42 specimens (84%). No anastomotic loop was found in 8 (16%). Of the arteries supplying the duct, the most frequent are the posterior superior pancreaticoduodenal (100%), the right hepatic artery (84%), the posterior inferior pancreaticoduodenal (56%), the right gastric (44%), and the common hepatic (40%). There was a pronounced variation in the patterns. Suggestions are given to minimize disturbance of the blood supply during surgery on the common duct.

LEMUEL C. MCGEE

STERLING, J. A. Diverticula in the terminal portion of the common bile duct. *Am. J. Path.*, 25: 325 (Mar.) 1949.

The author carefully studied the terminal portion of the common duct in 70 postmortem specimens. In 7 per cent of the cases, abnormal channels were found. Four diverticula and one choledochopancreatic fistula are reported. Two of the diverticula contained stones. Two of these cases had gross and microcopic evidence of pancreatitis. It is suggested that diverticula of the common duct may be a factor in the pathogenesis of pancreatitis.

DAVID A. DREILING

HICKEN, N. F., STEVENSON, V. L., ALLEN, L. M., and CORNWALL, C. R. Double gall-bladders. A report of four cases, one with suppurative cholangitis and bacteremia. *Surgery*, 25: 431 (Mar.) 1949.

A true "double" gall bladder denotes a complete duplication of the vesica fellea,

each unit of which is drained by its own cystic duct. The cystic duct unites with the common hepatic and choledochal ducts at variable locations. As a rule, the gall bladders are not contiguous. There is no characteristic clinical syndrome which permits differentiation from other cholecystopathies. Two distinct gall bladder shadows or two distinct rows of gall stones have been noted. Differentiation from various malformations of the gall bladder may be made by taking cholangiograms in several views and positions. Cholangiographic studies have also revealed this condition.

Four cases are reported and illustrated by the authors. Two were diagnosed by cholangiograms, one by cholangiograms and the other at laparotomy.

MARCEL PATTERSON

SMYTH, M. J. Congenital absence of the gall-bladder. *Lancet*, 256: 301 (Feb.) 1949.

Congenital absence of the gall-bladder is a rare anomaly and is usually associated with gross malformations of the extrahepatic ducts. Two theories have been advanced to explain this condition: (1) The bile ducts and liver normally develop as a diverticulum from the fore-gut in the fetus, and the gall bladder and cystic ducts develop as an outpocket from this diverticulum. Thus, a failure of the latter, would result in complete absence of the gall-bladder. (2) The bile ducts and gall-bladder are the first hollow organs. Their lumen is later obliterated, and finally they become re-canalized. An arrest in the final stage of development may lead to a congenitally absent gall-bladder.

The patients, with congenital absence of the gall-bladder who have come to operation, presented the clinical features of cholecystitis and lithiasis. X-rays revealed a non-visualization of the gall-bladder. A case is presented of a 72-year old female with symptoms of cholelithiasis. At operation, the common bile duct was found to be greatly dilated and contained a large stone. This was removed and a T-tube was inserted for drainage. Several days later, cholangiography revealed dilated ducts but no gall-bladder. The patient made an uneventful recovery.

PHILIP LEVITSKY

FRIEDRICH, L. and POLICZER, M. Use of thrombin in liver puncture. *Lancet*. 256: 523 (Mar.) 1949.

The authors inject commercial thrombin through the biopsy needle to prevent hemorrhage. The thrombin is in powder form, which is dissolved in a solvent containing pyrocatechin and calcium chloride to enhance thrombin activity, and sodium chloride and tricesol to ensure sterility and stability. The proportions are 200 units per 1 ml of solvent. The liver puncture needle consists of an outer needle 12 cm. long with a 2 mm. bore, and an inner needle with a 1.4 mm. bore. The outer needle is graduated in cms. and has a depth screw. The biopsy needle must not enter the liver any deeper than 2-3 cms. below the capsule because large branches of the portal vein run at a depth of 4-5 cms. After the liver tissue is aspirated according to the procedure described, the thrombin solution is injected. To date, 200 cases have been biopsied with no untoward symptoms.

PHILIP LEVITSKY

CAPPS, R.B. AND NORCROSS, P. Hepatic insufficiency. *Med. Clinics No. Amer.*, 447 (March) 1949.

Hepatic injury may be produced by various causes, and frequently results in chronic hepatic disease. Chronic viral hepatitis, amebiasis, malaria, infectious mononucleosis, brucellosis and toxic hepatitis are the main causes. Recent opportunity to study cases of viral hepatitis has advanced knowledge of clinical hepatic response not only to the virus but also to other injurious agents, since their results in the liver are similar.

Viral hepatitis, in which evidence of hepatic damage persists for more than three months after the acute onset, is termed chronic. The chronic condition develops, generally, because of inadequate treatment. Persons with previous hepatic damage, secondary infections or malnutrition also seem particularly susceptible to this. The acute attack is often mild and without jaundice. In chronic viral hepatitis, with exception of the cholangiolitic form, clinical jaundice is usually absent. Absence of hepatic tenderness, tolerance to exercise, and relative ab-

sence of symptoms differentiate the inactive from the active form. Differentiation from chronic cholecystitis, functional gastrointestinal disorders, psychoneurosis and other etiologic types of hepatitis is discussed.

Treatment of chronic viral hepatitis is based on rest, diet, avoidance of additional hepatic trauma, and elimination of foci of infection. The latter is stressed. No emphasis is placed on elimination of fat or on excessive increase of protein intake. Lipotropic substances are not considered to be of advantage.

L. T. ROSENTHAL

DE PAULA E SILVA, G. S. A simple method for computing the volume of the human gallbladder. *Radiol.*, 52: 94 (Jan.) 1949.

The author describes a simple method of computing the volume of the gall bladder. A tracing of the cholecystogram, made on transparent paper, is placed upon a ruled paper with parallel and equidistant lines, thus dividing it into a series of segments or "disks". The diameters of these segments are measured in millimeters and the volumes corresponding to the diameters of these segments are found in an accompanying table. The sum of these individual volumes is multiplied by a correction factor to compensate for magnification of the image shown in the film, and the result is the volume of the gall bladder in cubic centimeters.

FRANZ J. LUST

PANCREAS

PACK, G. T. AND BOOHER, R. J. Surgical problem of periampullary cancer. *Arch. Surg.*, 57: 71 (July) 1948.

The authors' experience with 5 cases of periampullary cancer is presented. This type of tumor affords the greatest hope of cure with total duodenectomy and resection of the head of the pancreas. The development of this operative procedure is reviewed. The procedure now generally accepted consists of a choledochojejunostomy performed proximal to the gastrojejunal anastomosis and a pancreaticojejunostomy. This allows for a radical resection and lessens the more frequent complications of pancreatic fistula and ascending cholangitis.

The following symptoms suggest this lesion: Gradual onset, jaundice, itching, insidious anorexia, weight loss, melena, and secondary anemia. An enlarged liver and palpable gall bladder are sometimes noted. The duration of the jaundice suggests an index to resectability and survival. The best results are noted when operation is performed shortly after onset. The diagnosis at the operating table is often difficult and uncertain.

MARCEL PATTERSON

GRAY, H. K. Carcinoma of the pancreas. Arch. Surg., 57: 763 (1948).

Ewing described the two chief types of malignancy of the pancreas, carcinoma of the ducts or cylindrical carcinoma, and carcinoma of the parenchyma. Lately, carcinoma of the islands has been discovered with increasing frequency. Pain is now recognized as a common feature of these neoplastic lesions and in carcinoma of the head, progressive jaundice and a distended gall bladder with acholia, form a reliable diagnostic complex. Recognition of carcinoma of the body or tail is more difficult because jaundice is usually absent. Laboratory data in non-obstructive pancreatic carcinoma have little diagnostic value. Fortunately, 60-70 per cent of neoplasms occur in the head of the pancreas. In obstructive jaundice, the differentiation between hepatogenous jaundice and that due to malignant biliary obstruction is essential since surgery will be harmful in the former condition. The authors present a complete table of differential diagnostic criteria. The spontaneous occurrence of the hypoglycemic syndrome should make islet cell tumor suspect. Marked cirrhoses of the liver and cases of hormonal insufficiencies almost never produce this symptom complex.

Similar preparations for surgery should be made in all cases of obstructive jaundice, whatever the cause. Surgery itself has included two recent advances. Firstly, the distal portion of the common bile duct is to be preferred over the gall bladder in the restoration of the flow of bile. Secondly, an effort should be made to re-implant the cut end of the remaining pancreas into the gas-

trointestinal tract. The latter measure takes advantage of what external secretion of the pancreas remains and discourages the development of pancreatic fistulae.

A. I. FRIEDMAN

BEHREND, M. AND BEHREND, A. Chronic pancreatitis causing complete and incomplete obstruction of the common bile duct. Arch. Surg., 57: 51 (July) 1948.

Ten patients with chronic pancreatitis are presented with a general review of the subject. In the authors' opinion, congenital fibrocystic disease of the pancreas in children may be a forerunner of chronic pancreatitis. Ascending infections from the duodenum or infection of the biliary tract may be inciting factors. Stones were found in the gallbladder or common duct in only one of these patients. The difficulty in diagnosis is emphasized. Indigestion, intermittent jaundice, diabetes mellitus, undigested food particles in the stool and calcareous deposits in the pancreas may point to the consideration of this condition.

The recommended treatment is an anastomosis of the common duct to a hollow viscus. This is preferred to the use of the T-tube after choledochostomy. In the authors' experience, anastomosis to the stomach has resulted in ascending cholangitis infrequently. In all operations on the biliary tract the pancreas should be palpated. The various grades of hardness found in pathologic conditions of the pancreas make it extremely difficult to make a proper diagnosis and exclude carcinoma. In all cases in which there is doubt as to the process, a biopsy specimen should be taken.

MARCEL PATTERSON

THOMAS, P. O. AND ROSS, C. A. Effect of exclusive parenteral feeding on the closure of a pancreatic fistula. Arch. Surg., 57: 104 (July) 1948.

This article is a case report of a 67-year-old man who developed a pancreatic fistula following a radical pancreaticoduodenectomy with cholecystojejunostomy and gastrojejunostomy. The fistula persisted for 8 weeks with no evidence of closure. Measurements on rate of flow of pancreatic juice

revealed that, on a regular diet, 50-625 cc. were excreted in a twenty-four hour period. A basal flow of 7.5 drops per minute to a maximum rate of 18-20 drops per minute, about 3 to 3½ hours after ingestion of a meal, was noted. The twenty-four hour output of water, sodium, potassium, chlorine, phosphorus and total nitrogen was measured in both the urine and pancreatic juice.

As a trial method of therapy, complete gastrointestinal rest with parenteral feedings was maintained. The observations on the chemical constituents of urine and pancreatic juice were continued. On daily parenteral feedings of 2000 cc. of dextrose, then dextrose and amino acid solutions, the 24-hour output of pancreatic juice was significantly smaller. With Amigen and dextrose solutions the output decreased progressively so that during the third day of Amigen therapy (twelfth day of treatment), the fistula closed and has remained closed. Alimentionation was maintained for 4 more days after which the patient took a regular diet by mouth.

It is concluded that effective water and nitrogen balance can be maintained for a considerable period of time with parenteral feedings. Pancreatic secretion is greatly suppressed after onset of complete gastrointestinal rest and actually inhibited by intravenous injections of hydrolyzed protein.

MARCEL PATTERSON

ANEMIAS

EPSTEIN, R. D. Cells of the megakaryocyte series in pernicious anemia: In particular, the effect of specific therapy. *Am. J. Path.*, 25: 239 (Mar.) 1949.

Bone marrow studies of 5 cases of pernicious anemia have been made with special emphasis on the morphology and number of the megakaryocyte series. Before remission, there was an increased number of polykaryocytes and a decreased number of mononuclear megakaryocytes; following remission, this cell ratio was reversed. The total number of cells of the megakaryocyte series was either normal or increased in the marrow of patients in relapse.

DAVID A. DREILING

ULCER

LUER, C. A. Acute perforations of stomach and small bowel ulcerations. *Surgery*, 25: 404 (Mar.) 1949.

A study is presented of 362 consecutive cases of acute perforation of the stomach and small bowel ulcerations, occurring during a 10-year period. There was an operative mortality of 18.2 per cent in the 318 patients treated surgically, the majority of whom were men. In the 17 female patients, the total mortality rate was 47.1 per cent, because of inadequate diagnosis. High mortality rates were also noted in older age groups because of atypical histories, physical findings, and delay in the patients' presenting themselves for treatment.

Fifteen per cent of the patients gave no previous history of gastrointestinal symptoms. Temperature, pulse, and respiratory rates were relatively normal in early perforations but increased with passage of time. Abdominal rigidity was noted in the majority of cases seen early, but occurred in less than half of the cases seen after 24 hours. Within 12 hours after perforation, half of the peritoneal cultures were sterile. As time elapsed, the number of positive cultures increased to over 75 per cent. The mortality rate increased progressively, from 5.9 per cent in those operated in the first 6 hours to 54.5 per cent in those in which surgery was delayed beyond 24 hours.

Duodenal and pyloric ulcers were the source of the perforations in 72 per cent, gastric ulcers in 25 per cent. Wound infection was the most frequent complication noted, particularly in those cases where drains were used. Pulmonary complications and intraperitoneal abscess were next in frequency.

MARCEL PATTERSON

NEUMAYR, A. AND SCHMID, J.: Magenschleim und Ulcusgenese (I. Mitteilung) [The relation of gastric mucus to the development of ulcer. I]. *Gastroenterologia*, 74: 121 (1948/49)

The gastric mucus obtained from patients suffering from peptic ulcer was found to contain smaller amounts of histamine-like substances than were present in control individ-

uals. The ability of gastric mucus, from patients with ulcer, to absorb histamine was considerably reduced. The absorptive capacity of mucus for histamine was found to be increased both in vivo and in vitro by Larostidin, Robuden and Antistine. The peptic activity of gastric juice was increased in vitro by the addition of histamine. The addition of Antistine, Larostidin and Robuden to gastric juice resulted in a reduction in peptic activity.

The results suggest the possibility that increased amounts of histamine in gastric juice associated with impaired absorption of the histamine by the mucus fraction may give rise to hyperacidity and hypermotility of the stomach. Increase in peptic activity also may occur as a result of the rise in histamine content of the gastric juice. These factors may bear an etiological relationship to peptic ulcer.

CHARLES A. FLOOD

GARLOCK, J. H. AND LYONS, A. S. The surgical therapy of duodenal ulcer. *Surgery*, 25: 352 (Mar.) 1949.

In an effort to evaluate the best surgical procedure for duodenal ulcer, 187 cases having had subtotal gastrectomy are reported by the authors. These cases have been personally observed from 1 to 13 years. The operative mortality was 2.1 per cent. Inability to gain weight was the most frequent postoperative complaint with only three instances of "dumping" syndrome. Three patients developed gastrojejunal ulcers.

The authors state that the most important aspect of the operation is the removal of the entire pyloric antrum and pyloric ring. Non-absorbable suture material for the duodenal stump and the use of a drain where extensive denudation occurs are the most important factors in reducing postoperative duodenal leakage.

Vagotomy alone does not remove the hormonal factors which may be the dominant cause of the reappearance of hyperacidity and ulceration. It is suggested that vagotomy and gastrectomy are the most logical procedures in cases of marked hyperacidity or repeated hemorrhages. Complete

vagotomy alone is recommended for those cases in which gastrojejunal ulcers occur following adequate gastrectomy.

MARCEL PATTERSON

HOLM, B. AND MACKAY, A.G. The effect of surgical devascularization of the stomach on the production of Mann-Williamson ulcers. *Surgery*, 25: 446 (Mar.) 1949.

Devascularization of the stomach by ligation of the major portion of the arterial supply of the organ has been proposed as a method of treatment for chronic duodenal ulcer. This procedure has been suggested as a "physiologic gastrectomy" with ischemic atrophy and diminished function of the chief and parietal cells of the gastric mucosa.

The authors evaluated this procedure by using 6 dogs in which all the arteries on the lesser curvature and approximately 9 out of 10 smaller vessels of the gastroepiploic vessels on the greater curvature of the stomach were ligated. This was combined with an immediate Mann-Williamson procedure in 2 dogs. In 4 other animals, this latter procedure was done 2 or 3 weeks later. In the 4 dogs that survived the operations, typical peptic ulcers occurred. The development of these ulcers was consistent with previous findings, in this laboratory, of minimal histological changes and no significant decrease in gastric acidity following devascularization. It is concluded that subtotal devascularization of the stomach failed to protect dogs from Mann-Williamson ulcers in this series.

MARCEL PATTERSON

MILSTEIN, B. B. Immediate results of partial gastrectomy for peptic ulcer. *Lancet*, 256: 514 (Mar.) 1949.

This report attempts to show that subtotal gastrectomy for peptic ulcer is a safe procedure even in the hands of junior surgeons. In a series of 101 unselected cases, the mortality rate was only 2 per cent. This is attributed to preoperative care, postoperative Wangensteen suction, and strict suture technique. Complications, on the other hand, were very high, being in the neighborhood of 50 per cent. Infection occurred in 17 per

cent; this can be reduced since it is preventable in many cases.

PHILIP LEVITSKY

SHIPLEY, E. R. AND WALKER, J. H. Perforated gastric and duodenal ulcers. An analysis of 200 consecutive cases. *Am. J. Surg.*, 77: 329 (Mar.) 1949.

This report is based on 200 consecutive cases of perforated gastric or duodenal ulcer admitted to the University Hospital, Baltimore from 1935 to 1946. White patients comprised 86% of the series, and negroes 14%; 93.5% were males, and 6.5 per cent were females. The youngest patient was 19 years and the oldest 76 years. The over-all mortality was 26 per cent. In 11 per cent of the series, perforation was the first symptom. Hematemesis occurred in 7.5 per cent. The abdominal findings as well as general appearance of the patient varied with the degree of peritonitis. Thirty-six per cent were stated to have been in "shock" on admission. The ulcer site was duodenal in 39.5 per cent, pyloric in 15 per cent, and gastric in 45.5 per cent.

The diagnosis was made correctly in 95.5 per cent based on previous history, the sudden onset of severe upper abdominal pain with board-like rigidity of the abdomen, and X-ray evidence of free air in the peritoneal cavity. Upright films of the abdomen were taken in only 48 cases to demonstrate free peritoneal air and were positive in 60.4 per cent. Most common mistaken diagnosis was acute appendicitis (3%). Cholecystitis with cholelithiasis was mistakenly diagnosed in 2 cases and coronary artery disease in 1 case.

Of the 200 patients, 12 were not operated upon either because they refused surgery or they were moribund on admission. During the period covered by this study, there has been a tendency toward the simplest method of repair. Gastric siphonage together with better parenteral feedings, earlier oral feedings, antibiotics and early ambulation have been instituted over the years with resultant declining mortality. The time elapsing between perforation and surgery greatly influenced the mortality rate. Surgical repair within 3 hours resulted in a 4.7 per cent mortality, and the mortality rate climbed to

100% for the 36-48 hour delay. If perforation had existed for 48 hours or more the mortality rate dropped to 50 per cent.

NATHAN SHAPIRO

LEHMANN, G. AND STEFKO, P. L. The action of Thephorin upon histamine-induced gastric secretion in dogs and on gastric ulcer formation in rats. *J. Lab. Clin. Med.*, 34: 372 (Mar.) 1949.

The effect of the anti-histaminic drug, Thephorin, was tested in dogs and rats. In dogs with denervated pouches, the gastric secretion induced by histamine was decreased about 30 per cent, which would correspond to the inactivation of 75% of administered histamine. Thephorin prevented, to a marked degree, formation of gastric ulcer in rats which were being given daily injections of histamine intramuscularly. Thephorin also prevented ulceration in rats prepared by the Shay method (ligation of the stomach after starvation.) Atropine also had a marked anti-ulcer effect under these conditions, but it did not prevent ulceration in rats to which histamine had been administered.

EDGAR WAYBURN

ALTHAUSEN, T. L. Prevention of recurrences in peptic ulcer. *Ann. Int. Med.*, 30: 544 (Mar.) 1949.

Statistics are cited to indicate that 46-93 per cent of ulcer patients have one or more recurrences within five years, and that 10-36 per cent have a recurrence within the first six months. Physical and mental fatigue, emotional upsets, dietary indiscretions, infections of the upper respiratory tract and seasonal influences are discussed as provocative factors in recurrences. Inadequate medical treatment is mentioned as another important cause.

A recommended regimen consists of frequent feedings of milk and cream every 2-4 hours) alternated with antacids for the first week. Antispasmodics are given at regular intervals for four months. Bland foods are added gradually until a modified general diet is tolerated—usually within three months. Antacids are given for at least six months. Bed rest is considered a controversial point.

Specific preventive measures are not avail-

able, although enterogastrone has hopeful possibilities. General preventive measures include education of the patient as to the cause, elimination of known inciting factors as overwork and emotional problems, avoidance of coffee and alcohol, restriction of smoking, and avoidance of infection. Immediate return to a strict protective regimen is advised when causes for recurrences are unavoidable. Recurrent epigastric distress should be treated promptly in consideration of the known high threshold for pain of these patients. Indications for and results of surgical intervention and adequacy of postoperative therapy are discussed.

L. T. ROSENTHAL

BAUMGARTNER, W. Vagotomic oder Splanchnicotomie zur Behandlung des peptischen Geschwüres? [Should peptic ulcer be treated by means of vagotomy or splanchnicotomy?] *Gastroenterologia*, 74: 156 (1948/49).

Supradiaphragmatic section of the splanchnic nerves is described as a treatment for peptic ulcer. The procedure is based on the hypothesis that patients with ulcer suffer primarily from sympathicotonia with which vagotonia is associated as a secondary phenomenon. After producing a pneumothorax, the splanchnic nerves are located through a thoracoscope and severed with a hot snare.

The author has treated 25 patients by splanchnicotomy. Twenty-four patients immediately became symptom-free. Severe constipation was present for the first week postoperatively but quickly cleared up. No other untoward effects were noted after operation. The long-term results from the procedure will be reported later.

CHARLES A. FLOOD

PROCTOLOGY

WHITNEY, E. T. Bleeding per ano. *Am. J. Dig. Dis.*, 16: 91 (Mar.) 1949.

Although bleeding by rectum usually evokes in the patient's mind the fear of cancer, it is a fact that nearly every proctological ailment is accompanied by bleeding, either routinely or occasionally. There are, therefore, about 100 entities which need to be taken into consideration whenever a

patient complains of rectal bleeding. These may be classified under the general headings of hemorrhoids; ulcers about the anus; ulcerations above the anus; and tumors of the anus, rectum or sigmoid. The diagnostic approach to this problem includes consideration of the duration of the bleeding and of its type and amount. Bleeding, prolonged over a number of years, usually indicates a non-malignant cause. Slight bleeding is generally of only minor significance, while active bleeding usually signifies a ruptured prolapsing internal hemorrhoid. The presence of clots mixed with the stool usually indicates trouble above the hemorrhoidal area. Explosive bleeding with mucus often signifies the existence of marked organic disease in the rectum or lower sigmoid, either colitis or malignancy. Severe pain associated with the bowel movement strongly suggests the presence of fissure in the posterior commissure. Change in bowel habit points strongly to malignancy; diarrhea associated with the bleeding and its diagnostic significance should also be considered. The author emphasizes, however, the need for restudy of all patients with bleeding, this study to include visual and digital examination of anal area, anoscopic and sigmoidoscopic examination, studies of the stool, and barium enema, as well as specific studies such as the Frie test. The article also emphasizes that although bleeding by rectum may be due to numerous relatively minor disturbances, only the most thorough study will serve to exclude the presence of malignant disease as its cause.

HENRY TUMEN

SURGERY

VANDERHOOF, E. S. AND MERENDINO, K.A. Unfavorable reactions to oxidized cellulose (oxycel) in the bed of the gallbladder. *Arch. Surg.*, 58: 182 (Feb.) 1949.

Earlier reports on the use of oxidized cellulose for tissue hemostasis show little tissue reaction and complete absorption or dissolution of the material. Only 3 cases have heretofore been reported in which oxidized cellulose has been implanted in the bed of the gallbladder and left *in situ*.

The authors present case reports on 3 out

of 4 patients treated in this fashion during cholecystectomy. Each patient had a febrile reaction with subhepatic tenderness and leucocytosis a week or more after surgery. One developed an abscess which required surgical drainage. This experience raises a doubt as to the desirability of using such "permanent" hemostasis in the bed of the gallbladder.

LEMUEL C. MCGEE

BREIDENBACH, L. AND SLATTERY, L. R.

Construction and care of the permanent colostomy. *Am. J. Surg.*, 77: 344 (Mar.) 1949.

While most features of the Miles abdominoperineal resection for carcinoma of the rectum have become standardized, the construction of the end colostomy varies with the surgeon. Because of this variability, the results have not been uniformly good and structural defects have followed. In addition, the authors have found many patients inadequately trained to handle a permanent colostomy. These two difficulties have resulted in the use of colostomy bags for which there should be no need. Most patients object more to the colostomy "bag" than to the abnormal opening. Consequently many patients turn to sphincter-saving operations and force the surgeon to compromise with less radical surgery than the cancer requires.

A method for constructing an end colostomy is described which has yielded very satisfactory results. One essential feature is the suturing of the appendices epiploica to the abdominal layers of the wound, thereby stabilizing the bowel. Another feature is that sufficient room be allowed for one's index finger to fit comfortably in the peritoneal opening beside the bowel at the time that the colostomy is constructed. The third feature of the method described is the fact that 2 or more inches of the bowel are allowed to protrude above the skin level when the incision is closed. In most cases the colostomy is sutured to a paramedian or rectus splitting incision and there is no danger of herniation of small bowel under these circumstances and hence no need for obliteration of the lumbar gutter. When the

loop is brought through a stab wound in the left lower quadrant, closure of the lumbar gutter is necessary.

A new type of colostomy irrigator is described with illustrative pictures. When the colostomy is properly constructed as herein described and the patient is properly instructed, there is no need for a colostomy bag.

NATHAN SHAPIRO

PHYSIOLOGY: SECRETION

MAHL, G. F. Effect of chronic fear on the gastric secretion of HCl in dogs. *Psychosomatic Med.*, 11: 30 (Jan.-Feb.) 1949.

Emotional factors are now regarded as playing a primary role in the etiology of peptic ulcers. However, the specific nature of these psychogenic factors is not yet agreed upon by the various investigators. Repressions, frustrations, anxieties, resentment, guilt, fear, hostility and various tensions, have been found to characterize the psychogenic make-up of ulcer patients. On good grounds, the author advances the idea that fear plays an important role as an emotional factor for the causation of peptic ulcer. Certain experiments have shown that fear is associated with an increased secretion of HCl mediated through the vagus nerve. This finding is in distinct contrast to Cannon's hypothesis of the emergency function of emotions, in which he proposed that, in fear, HCl secretion would be decreased or inhibited completely.

Seven dogs were employed and their normal behavior patterns were noted. Control determinations of gastric acidity, gastric emptying time, and heart rate were made. Gastric juice was obtained by means of stomach tube. A buzzer was sounded periodically to condition the animals; fear was induced by electric shocks in definite relation to the buzzer sounds. The electric shocks were delivered through special grids making up the floor of the animal's cage. The various observations are described elaborately. Six out of the seven dogs developed chronic fear behavior, and at the same time showed increased gastric acidity, gastric emptying rate, non-resting heart rate and increased variability of both resting and non-resting

heart rates. Removal of the animals from the experimental environment resulted in return to normal. The direct extension of Cannon's hypothesis to chronic emotional states, which are of basic importance in psychosomatic disorders, is not valid.

FRANK NEUWELT

PHYSIOLOGY: MOTILITY

WATKINS, D. H. AND MANN, FRANK C.
Motor responses of spatially transposed intestinal loops. *Surgery*, 25: 393 (Mar.) 1949.

Using dogs, the behavior of an exteriorized intestinal loop, before and after transposition to another site of the intestinal tract, was studied in respect to the rate of rhythmic contractions and the time of feeding response. It was found that the number of rhythmic contractions per minute of any individual loop remained remarkably uniform. There was a uniform decrease from 17-18 per minute at the ligament of Treitz, to 11-12 per minute near the ileocecal valve. After transplantation, the rate of rhythmic contractions was seen to decrease by 1 or 2 contractions per minute regardless of whether the loop was transplanted higher in the tract than originally or not. The interval from feeding to motor response in the loop varied directly as the distance from the pylorus. This was found to occur regardless of the site of transplantation of the loop; i.e. jejunum with a normal 1-3 minute feeding reaction time increased to 8-12 minutes after being transplanted to the ileum.

It is concluded that the feeding reaction response does not depend on the integrity of the mesenteric nerves, and that some form of motor activity passes down the length of the small intestine after feeding. The rate of rhythmic contractions appears to be an inherent property of the loop and does not depend on intestinal continuity.

MARCEL PATTERSON

ANATOMY

ELIAS, H. A re-examination of the structure of the mammalian liver. I. Parenchymal architecture. *Am. J. Anat.*, 84: 311 (Mar.) 1949.

Our general concept of the mammalian

liver is that it is composed of cords of hepatic cells, and that a bile capillary runs through the axis of a cord. The author had occasion to examine liver structure critically, in order to present the material for teaching purposes. A stereographic or three-dimensional visualization of the liver was built up from its microscopic constituents. The author soon found that the hepatic cell cord idea did not hold for the structure of the liver. Livers were studied from 5 human beings, 3 cats, 3 rabbits, and 3 horses. Embalmed livers were found best for this study. The "laminae hepatis" invariably are one cell thick and are perforated at many places; the size of these stomata varies. Furthermore, these liver sheets are curved rather than straight. Two types of livers were distinguished: the saccular liver, as present in man and cat, and the tubular liver of the horse and rabbit. The dog liver is transitional between these two types. The relative storage capacity for blood is greater in the saccular than in the tubular type. The laminae hepatis anastomose with one another, and the enclosed spaces contain the sinusoids. These spaces (lacunae hepatis) form a continuous labyrinth (labyrinthus hepatis). The lacunae hepatis are shaped like wide sacs with flexible walls in the human and cat livers (hepar vasculare), in contrast with the narrow and cylindrical spaces in horse and rabbit livers (hepar tubulare).

FRANK NEUWELT

DUNPHY, J. E. Surgical anatomy of the anal canal. *Arch. Surg.*, 57: 791 (Dec.) 1948.

An exact knowledge of the anatomy of the anal canal is necessary for the proper treatment of the surgical pathology that may develop. The external sphincter is a cylindric muscle that surrounds the anal canal, the internal sphincter and the longitudinal muscle. It is composed of three distinct portions separated by fibro-muscular septa which are prolongations inferiorly of the longitudinal muscle. Fibrosis of the subcutaneous portion, encountered in the constipated, produces a tight annular ring at the entrance to the anal canal, erroneously referred to as "pectinosis." Division of this band results in complete relief.

The branching fibro-muscular septa are the natural channels along which abscesses arising in the anal glands yield fistulae to the skin. Since 95 per cent of anal fistulae and ischio-rectal abscesses originate in the anal crypts, excision of the entire tract can be done without endangering the ano-rectal ring, i.e. the cephalic end of the anal canal where the internal sphincter, the longitudinal muscle, the levator ani posteriorly, and the deep portion of the external sphincter anteriorly join. But, in reality, the anal glands arising in the anal crypts and running deep into the internal sphincter must be identified and excised before fistulae can be completely eradicated. Only pathology above the anal canal produces fistulae which may necessitate a two-stage operation.

A. I. FRIEDMAN

MISCELLANEOUS

SPELLBERG, M. A. AND ZIVIN, S. Lymphosarcoma of the gastrointestinal tract. With a report of twenty-one cases. *Arch. Int. Med.*, 83: 135 (Feb.) 1949.

The authors reviewed the cases of primary gastric and primary intestinal lymphosarcoma observed in a large veterans' hospital during a fifteen-year period. They report eleven cases of primary gastric lymphosarcoma and ten cases of primary intestinal lymphosarcoma. The incidence of lymphosarcoma was 1 case of primary gastric lymphosarcoma to 88 cases of gastric carcinoma, and 1 primary intestinal lymphosarcoma to every 300 colonic carcinomas.

Roentgenologic examination usually failed to establish the diagnosis of gastric lymphosarcoma; gastroscopy was of some help. The prognosis of the small cell type of lymphosarcoma of the stomach was better than that of the reticulum type. In general, the prog-

nosis of gastric lymphosarcoma was better than that of gastric carcinoma. The treatment of choice was resection followed by irradiation. The prognosis of lymphosarcoma of the intestine was poor. No patient survived five years; most died in less than six months.

EDGAR WAYBURN

BASTENIE, P. A. AND KOWALEWSKI, K. P.

Les troubles gastro-intestinaux dans l'insuffisance thyroïdienne [Gastrointestinal disorders in hypothyroidism] *Gastroenterologia*, 74: 225 (1949).

Eighty-five patients with hypothyroidism, of whom 60 had frank myxedema, were studied to determine the incidence of associated gastrointestinal disorders. The majority of the patients suffered from anorexia. Hypochlorhydria or achlorhydria was found in most patients in whom a gastric analysis was done. The authors believe that the hypochlorhydria probably results from mucosal atrophy in the stomach.

Disorders of the liver or gallbladder were encountered in 21 per cent of the cases. These included cases of cholecystitis with or without gallstones, fatty liver and cirrhosis. It is believed that the gallbladder disease in hyperthyroidism is related to the disturbance in cholesterol metabolism.

Marked dilatation or elongation of the colon was observed in many patients. Constipation and abdominal distention were frequent complaints and a few patients developed paralytic ileus. In two patients with paralytic ileus, the picture was rapidly controlled by treatment with thyroxin. Pathologically, atrophy of intestinal mucosa with inflammatory changes in the submucosa was observed in patients who came to autopsy.

CHARLES A. FLOOD

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